International Journal of Medical Science in Clinical Research and Review
Online ISSN: 2581-8945
Available Online at http://www.ijmscrr.in Volume 7|Issue 02 (March-April) |2024 Page: 304-309

Original Research Paper

Incidence Rates of Endocrine Complications in Polytransfused Beta-Thalassemia Patients

Authors:
M. Noumi[1], A. Himeur[2], A.khaptani[1], Y.Ferhani[1], R. Boukari[1]
[1]Mustapha Bacha University Hospital Centre, Pediatrics Department
[2]CPMC endocrinology laboratory.
Corresponding Author*:*
M. Noumi
Mustapha Bacha University Hospital Centre, Pediatrics Department

Article Received: 01-January-2024, Revised: 12-January-2024, Accepted: 02-February-2024

ABSTRACT:

Introduction: β-thalassemia is a hereditary chronic hemolytic anemia characterized by a defect in the synthesis of beta-globin chains, which is particularly common in the Mediterranean region, southern Asia, and the Middle East. Transfusion programs and chelation treatment have considerably extended the life expectancy of patients. This has led to an increase in the prevalence of cardiac, hepatic and endocrine complications. **Objectives:** Describe the frequency of endocrine complications in patients with polytransfused β-thalassemia. Study the relationship between endocrine complications and ferritin levels. **Method:** It's a **transversal descriptive, analytical and monocentric study** which was carried out in the Mustapha University Hospital pediatric department and which involved 87 patients with beta thalassemia major (46 Girls and 41 Boys), most of whom were regularly followed for several years, and treated with a transfusion regimen (**more than 10 transfusions**) combined with chelation therapy. All patients were evaluated by a clinical history, a physical examination, measurement of height and weight, and evaluation of pubertal development stage. To assess glucose tolerance, fasting blood glucose and an oral glucose tolerance test (OGTT) were performed. Serum levels of free T4 (FT4), thyroid-stimulating hormone (TSH), calcium, phosphorus, and parathyroid hormone (PTH) were also measured. **Results:** Growth delay was observed in sixteen cases (18.4%). Hypothyroidism was observed in sixteen cases (18.4%). Twenty-eight patients (32%) developed glucose regulation disorders, with 16 (18.4%) having moderate fasting hyperglycemia (HGM), nine (10.3%) showing glucose intolerance (IG), and 4 patients (4.6%) developing diabetes. Two patients (2.3%) had hypoparathyroidism. Hypogonadism was the most frequent complication, observed in 72% of the pubertal population. Over 90% of them experienced pubertal delay, 17.4% of patients had secondary amenorrhea, 13% had primary amenorrhea, and 8.7% experienced menstrual irregularities. **Conclusion:** Despite chelation therapy, the risk of endocrine dysfunction remains common in patients who have transfusion-dependent β-thalassemia. Hypogonadism was the most common endocrine complication.

Keywords: Endocrine complications, polytransfused β-thalassemia

INTRODUCTION:

Beta-thalassemia is a chronic hereditary hemolytic anemia characterized by a defect in the synthesis of beta-globin chains. It is particularly prevalent in the Mediterranean region, southern Asia, and the Middle East.(1). Transfusion programs and chelation treatment have considerably extended the life expectancy of patients(2). This has led to an increase in the prevalence of cardiac, hepatic and endocrine complications associated with iron overload (3). Endocrine complications, through direct damage to the glandular parenchyma or the hypothalamic-pituitary axis (4), lead to hypogonadism (5), short stature (6), hypothyroidism (7), hypoparathyroidism (8), glucose intolerance (GI), and diabetes mellitus (9). Several studies have been carried out around the world to evaluate these endocrine complications. An Italian multicenter study (1994) on 1861 patients and 25 β-thalassemia centers (10), shows a prevalence of hypogonadism of 49%, diabetes at 4.9%, hypothyroidism at 6.2%, and hypoparathyroidism at 3.6%. The Toumba multicenter study in Greece (2007)(11), on 435 thalassemia patients, found a prevalence of growth retardation at 35%, hypogonadism at 32.5%, hypothyroidism at 5.9%, diabetes at 9.4%, and hypoparathyroidism. at 1.2%. An international study was carried out by De Sanctis on a large series of children and adolescents (3817 patients) suffering from β-thalassemia (12)in different regions of the world; the frequency of hypogonadism is 40.5%, growth delay 30.8%, the frequency of growth hormone deficiency (GHD) is 7.9%, hypothyroidism 3.2% ,

diabetes of 3.2%, glucose intolerance (GI) of 6.6%, and hypoparathyroidism of 6.9%.

Early recognition and treatment of endocrine complications are crucial to avoid irreversible late sequelae. Thus, it is important to know the incidence of endocrine complications in β-thalassemia in order to implement recommendations for the screening and management of these complications. It is with this aim that our work is devoted to the evaluation of the frequency and the description of the main endocrine complications of B-thalassemia.

MATERIALS AND METHODS:

It's a transversal descriptive, analytical and monocentric study which was carried out in the Mustapha University Hospital pediatric department and which involved 87 patients with beta thalassemia major (46 Girls and 41 Boys), followed regularly for several years for the most part, and treated with a transfusion regimen (more than 10 transfusions) combined with chelation therapy.

All patients are on a transfusion program, with the objective of maintaining the hemoglobin level above 9g/dl associated with chelation therapy; In our department, prior to 2008, deferoxamine (DFO) was the only available chelator, administered intravenously at a dose of 40 mg/kg/day. It was then replaced between 2008 and 2011 by deferiprone (DFP) administered orally. Since 2011, we have been using Deferasirox (DFX) orally. DFX is prescribed when serum ferritin level exceeds 1000 ug/l at a dose of 20 mg/kg/day; this dose is maintained as long as ferritinemia is controlled (< 2500 ug/l). In patients whose serum ferritin exceeds 2500 ug/l, an increase in the dose of DFX to 40 mg/kg/day is recommended. After 3 months of treatment, if the ferritin level remains above 2500 ug/ml, DFO is combined at a dose of 40 mg/kg/day subcutaneously 5 days a week until the ferritin level values drop below of 2500 ug/ml. The availability of chelation treatment is ensured by the Hospital's central pharmacy; we have not noted any interruption in the distribution of the drug. Hematological data, including markers of iron overload, were collected from patient records. These included the total quantity of blood units received, type of chelation therapy, pre-transfusion hemoglobin, comorbidities, and serum ferritin levels. All patients were evaluated by a clinical history, a physical examination, a measurement of height and weight for the assessment of short stature, and evaluation of pubertal development stage. To assess glucose tolerance, fasting blood glucose and an oral glucose tolerance test (OGTT) were performed. Serum levels of free T4 (FT4), thyroid-stimulating hormone (TSH), calcium, phosphorus, and parathyroid hormone (PTH) were also measured. Short stature is defined as a height less than 2 standard deviations below the average height for age and gender on the WHO growth charts, with a discrepancy between the patient's height and the target height greater than 1.5 standard deviations (13). In hypogonadism the clinical presentation can range from a delay in the onset of puberty to pubertal arrest and complete failure of puberty (14) (Table 1).

The diagnoses of diabetes mellitus and glucose intolerance were made according to the criteria of the American Diabetes Association (ADA) (15). Moderate fasting hyperglycemia was defined as fasting blood glucose ≥1 and <1.26 g/l (5.6-7 mmol/l) and <1.4 g/l (7.8 mmol/l) two hours after glucose load. Carbohydrate intolerance was defined as fasting blood glucose <1.26 g/l (7 mmol/l) and blood glucose ≥1.40 and <2 g/l (7.8-11.1 mmol/l) two hours after glucose load. Diabetes was diagnosed if fasting blood glucose was ≥1.26 g/l (7 mmol/l) on two occasions or ≥2 g/l (11 mmol/l) two hours after glucose load.

In primary hypothyroidism, subclinical hypothyroidism is defined by a normal T4 level with a slightly increased TSH level but < 10 U/ml. Patent hypothyroidism is characterized by a low T4 value with a significantly increased TSH >10 U/ml. Central hypothyroidism is defined by low T4 associated with low or normal TSH (16).

Hypoparathyroidism is defined by a normal or low PTH level (< 15pg/ml) in the presence of hypocalcemia with hyperphosphatemia (17). A serum ferritin value > 2500 g/l was considered as an indicator of severe iron overload.

Statistical analysis was carried out using SPSS 23 software. A descriptive analysis was carried out (mean ± standard deviations and/or medians, for quantitative variables and percentages for qualitative variables). The statistical tests of chi2, Fisher, Student, Wilcoxon-Mann-whitney, ANOVA were used for comparisons of 2 or more variables, and the analysis was completed by carrying out a logistic regression. The statistical significance threshold was set at 0.05. The bibliography was automatically generated by Zotéro using the Vancouver style.

For girls: • Pubertal delay is defined by the absence of breast bud development after the age of 13. • Arrested puberty: any stagnation at the same pubertal stage for more than 2 years. • Primary amenorrhea is defined as the absence of menarche beyond the age of 16. • Secondary amenorrhea is defined as the absence of menstruation for more than 3 months in a previously regular menstrual cycle. • Menstrual irregularities.
For boys: • Pubertal delay is considered by the absence of testicular enlargement, with a diameter < 2.5cm beyond the age of 14.

Table I: Definition of Hypogonadism

RESULTS:

Our study included 87 cases of β-thalassemia, all patients were enrolled at Mustapha University Hospital; more than 50% of them came from different regions of the country, namely 31% from the East of the country, 25% from the West and 2.3% from the South. The average age was 11.2±5.8 years with a range from 2 to 25.7 years old, 25% of patients were over 15 years old. Both sexes were equally represented in our series with 46 girls and 41 boys and a sex ratio of 0.9.

The average duration of blood transfusion in our population (reflecting the follow-up duration of these patients) was 10 years with extremes ranging from 6 months to 24.7 years; 77% of patients had a transfusion rate of less than 4 weeks, and 31% had an average transfusion volume exceeding 250 ml/kg/year. Splenectomy was performed in 40% of our patients.

The average serum ferritin level was 1653.16±1272ug/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 iron overload (ferritin > 2500 ug/l).

Short stature (height <-2SD) was detected in 16 patients (18.4%); bone age delay greater than 02 years was present in all these patients with growth delay. Among the 16 patients with short stature, 6 (37.5%) had severe growth delay (<-3DS). Eight girls (50%) and 8 boys (50%) were affected by growth delay; we did not find a statistically significant difference between boys and girls (P = 0.79). The average age of patients with growth delay is 16.3±5.6 years, while the average age of patients with normal height is 10.1±5.28 years, there is a statistical relationship significant between age and growth delay (p=0.00), (OR=44.16). Seven (43.8%) patients with short stature have a serum ferritin level above 2500 µg/l and 9 patients have a level below 2500 µg/l; there is a statistically significant correlation between serum ferritin level and growth delay (P=0.012), (OR=4.2).

Delayed puberty was the most frequently observed disorder in 21 (91%) patients, with a female predominance, 13 (62%) versus 8 (38%) boys. The other manifestations of hypogonadism in our series were secondary amenorrhea in 4 (17.4%) cases, primary amenorrhea in 3 (13%) cases, and menstrual irregularity in 2 cases (8.7 %). Five (21.7%) patients with hypogonadism had severe iron overload with serum ferritin >2500, while 18 (78.3%) patients had minimal to moderate iron overload; there is no significant relationship between hypogonadism and serum ferritin level (p=0.49). 21(91.3%)

OGTT was performed in 84 patients, and not performed in 3 patients, who had diabetes before the start of the study; 28 (32.2%) patients presented with glycoregulation disorders, 16 (18.4%) patients presented with moderate fasting hyperglycemia (MFH), 8 (9.2%) patients with GI, 4 (4.6%) %) patients with diabetes. 17 (60.7%) girls and 11 (39.3%) boys, there is no statistically significant relationship between the two sexes (p=0.31).

The average age of patients with glycoregulation disorders was 13.4±6.58 years, compared to unaffected patients, 10.2±5.2 years; there is a statistically significant correlation between the two groups (p=0.01). Among the 28 patients with glycoregulation disorders, 5 (27.8%) presented with severe iron overload (serum ferritin > 2500 µg/l), the other patients presented with moderate to slight overload; there is no statistically significant relationship between ferritinemia and glycoregulation disorders (p=0.65).

Primary hypothyroidism was present in 16 (18.4%) patients; the mean age of patients with hypothyroidism was 12±5.3 years, compared to the mean age of children with euthyroidism of 11±6 years; there is no significant difference between hypothyroidism and the age of the patients (p = 0.54). Hypothyroidism was

observed in 11 (68.8%) boys and 05 (31.3%) girls with (OR = 3); but there is no significant difference between girls and boys (p=0.055).

Among 16 (18.4%) patients who presented with hypothyroidism, 12 (13.8%) patients presented with subclinical hypothyroidism and 04 (4.6%) patients presented with overt hypothyroidism. Hypothyroidism was asymptomatic in all β-thalassemia patients at diagnosis, no patient had goiter, and no central hypothyroidism was observed. Among the 16 children with thyroid dysfunction, eight children had severe iron overload with serum ferritin > 2500 µg/l; there is a significant difference between hypothyroidism and ferritinemia (p=0.001) (OR=6.1).

Two patients (2.3%) presented with hypoparathyroidism with an average age of 25 years. In our study, one patient had severe iron overload, and the other patient had mild iron overload, but we were unable to establish a correlation between HPT and serum ferritin, due to the limited number of patients with HPT.

N: patients	87
Average age (year)	11.2 years
Ferritinemia (µg/ml)	1653.16±1272
Growth delay (%)	18.4
Hypothyroidism (%)	18.4
Hypoparathyroidism (%)	3.2
Glucose Regulation Disorders (%)	32
Hypogonadism (%)	72

Table 2: Summary of Endocrine Complications in Our Patients

n: patients	**87**	**Serum Ferritin**	**Multi varied**
Growth delay (%)	18.4	0.012	ORa = 18.37. P=000
Hypothyroidism (%)	18.4	0.001	ORa =6.1. P=0.003
Hypoparathyroidism (%)	3.2		
Glucose regulation disorders (%)	32	0.65	
Hypogonadism (%)	72	**0.49**	

Table 3: association between endocrine complications and serum ferritin levels

DISCUSSION:

Our study involved 87 polytransfused β-thalassemia patients (41 boys and 46 girls), with an average age of 11 years, regularly transfused, and undergoing oral chelation therapy such as Deferasirox (DFX). All patients had an assessment of their hormonal status: growth, puberty, thyroid, parathyroid glands, and glycemic balance. Assessment of iron overload status was carried out by measuring serum ferritin concentration. Fifty-five percent of patients had at least one endocrine complication, and 22% had two complications. Growth delay was observed in sixteen cases (18.4%) with an average age of 16.3 years, growth hormone deficiency (GHD) was confirmed in 3 cases (3.4%). Hypogonadism was the most frequent complication, observed in 72% of the population of pubertal age, with an average age of 18 years; more than 90% of them had delayed puberty, 17.4% of patients had secondary amenorrhea, 13% of patients had primary amenorrhea, and 8.7% of patients had menstrual irregularities. Twenty-eight patients (32%) developed glucose regulation disorders with an average age of 13.4 years, 16 (18.4%) patients an FHG, nine (10.3%) patients an GI, and 4 patients developed (4.6%) diabetes. Hypothyroidism was observed in sixteen cases (18.4%) with an average age of 12 years. It was subclinical in 12 patients (13.8%), and overt in four patients (4.6%). Two patients (2.3%) presented with hypoparathyroidism with an average age of 25 years. (Table 4) There was no evidence of gender predominance in endocrine complications, although the female gender was more frequent in hypogonadism and glucose regulation disorders, and the male gender more frequent in hypothyroidism. These complications were observed in 80% of the cases starting from the age of 10, the complications observed in children under 10 were mainly FHG and subclinical hypothyroidism.(18.19). After logistic regression, serum ferritin represents a risk factor in endocrine complications for a threshold greater than 2500 ug/l in hypothyroidism (ORa =6.1. P=0.003) and delayed growth (ORa = 18.37. P = 000).

	Cyprus 2007 (11)	Italy 1995 (10)	Iran 2003 (20)	TIF 2004 (12)	North America 2004 (21)	India 2014 (22)	Our results
Number of patients	435	1861	220	3817	342	89	87
Mean age (years)		15	15.2 ±3.1	13	20 (1-51)	13.6 (10–18)	11.2
Mean serum ferritin ug/l			1441		1710	3294	1653 ±1272
Hypogonadism (%)	32.5	49	35.1	40.5	35	51.1	72
Growth delay/GHD Review (%)	35		39.3	30.8		55	18.4
Hypothyroidism (%)	5.9	6.2	7.7	3.2	9	8.9	18.4
Hypoparathyroidism (%)	1.2	3.6	7.6	6.9	4	10.1	2.3
DM/GI (%)	9.4	4.9	8.7	3.2/6.5	10	13	4.6%/9.2

Table 4: Comparative prevalence of endocrine complications in children with β-thalassemia

CONCLUSION:

Our data underscore that endocrine complications in patients with β-thalassemia are very common and require close monitoring, especially in patients aged over 10 years. The measurement of serum ferritin levels correlates well with endocrine involvement and can be utilized to tailor chelation therapy for preventing these complications.

REFERENCES:

1. Cunningham MJ. Update on Thalassemia: Clinical Care and Complications. Pediatr Clin North Am. Apr 2008;55(2):447-60.
2. Brittenham GM. Iron-Chelating Therapy for Transfusional Iron Overload. N Engl J Med. 13 Jan 2011;364(2):146-56.
3. Vantyghem MC, Dobbelaere D, Mention K, Wemeau JL, Saudubray JM, Douillard C. Endocrine manifestations associated with inherited metabolic diseases in adults. Orphanet J Rare Dis. 2012;7(1):11.
4. Inati A, Noureldine MA, Mansour A, Abbas HA. Endocrine and Bone Complications in β-Thalassemia Intermedia: Current Understanding and Treatment. BioMed Res Int. 2015;2015:1-9.
5. Srisukh S, Ongphiphadhanakul B, Bunnag P. Hypogonadism in thalassemia major patients. J Clin Transl Endocrinol. Sep 2016;5:42-5.
6. Borgna-Pignatti C, Gamberini MR. Complications of thalassemia major and their treatment. Expert Rev Hematol. June 2011;4(3):353-66.
7. Ayoub N, Khaleel KJ, Mohammed II. Hypothyroidism in transfusion dependent β-thalassemia. 2016;9(1):5.
8. Basha N KP. Prevalence of Hypoparathyroidism (HPT) in Beta Thalassemia Major. J Clin Diagn Res. 2014;8(2):24-6.
9. Simcox JA, McClain DA. Iron and Diabetes Risk. Cell Metab. March 2013;17(3):329-41.
10. Italian Working Group on Endocrine Complications In Non-endocrine Diseases. Multicenter study on prevalence of endocrine complications in thalassaemia major. Clin Endocrinol (Oxf). June 1995;42(6):581-6.
11. Toumba M, Sergis A, Kanaris C, Skordis N. Endocrine complications in patients with Thalassaemia Major. Pediatr Endocrinol Rev PER. Dec 2007;5(2):642—648.
12. De Sanctis V, Eleftheriou A, Malaventura C, Thalassaemia International Federation Study Group on Growth and Endocrine Complications in Thalassaemia. Prevalence of endocrine complications and short stature in patients with thalassaemia major: a multicenter study by the Thalassaemia International Federation (TIF). Pediatr Endocrinol Rev PER. Dec 2004;2 Suppl 2:249—255.

13. Shehadeh N, Hazani A, Rudolf MCJ, Peleg I, Benderly A, Hochberg Z. Neurosecretory Dysfunction of Growth Hormone Secretion in Thalassemia Major. Acta Paediatr. August 1990;79(8-9):790-5.
14. De Sanctis V. Growth and Puberty and Its Management in Thalassaemia. Horm Res Paediatr. 2002;58(1):72-9.
15. American Diabetes Association. 2. Classification and Diagnosis of Diabetes. Diabetes Care. Jan 2017;40(Supplement 1):S11-24.
16. Chirico V, Antonio L, Vincenzo S, Luca N, Valeria F, Basilia P, et al. Thyroid dysfunction in thalassaemic patients: ferritin as a prognostic marker and combined iron chelators as an ideal therapy. Eur J Endocrinol. Dec 2013;169(6):785-93.
17. Sanctis VD, Soliman AT, Canatan D, Elsedfy H, Karimi M, Daar S, et al. An ICET-A survey on hypoparathyroidism in patients with thalassaemia major and intermedia: a preliminary report. 2017;88(4):435-44.
18. Pirinççio AG, Haspolat K, Söker M. Assessment of Thyroid Function in Children Aged 1-13 Years with Beta-Thalassemia Major. Iran J Pediatr. 2011;21(1):6.
19. Gulati R, Bhatia V, Agarwal SS. Early Onset of Endocrine Abnormalities in β-Thalassemia Major in a Developing Country. J Pediatr Endocrinol Metab. Jan 2000;13(6):651-6.
20. Shamshirsaz AA, Bekheirnia MR, Kamgar M, Pourzahedgilani N, Bouzari N, Habibzadeh M, et al. Metabolic and endocrinologic complications in beta-thalassemia major: a multicenter study in Tehran. BMC Endocr Disord. Dec 2003;3(1):1-6.
21. Cunningham MJ. Complications of -thalassemia major in North America. Blood. Jul 1, 2004;104(1):34-9.
22. Sharma R, Seth A, Chandra J, Gohain S, Kapoor S, Singh P, et al. Endocrinopathies in adolescents with thalassaemia major receiving oral iron chelation therapy. Pediatrician Int Child Health. Jan 2, 2016;36(1):22-7.