Original Article

Clinical and hematological features among β-thalassemia major patients in Jazan region: A hospital-based study

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Abstract

Context: Beta-thalassemia is a prevalent hereditary blood disorder in Saudi Arabia. Various clinical manifestations and hematological abnormalities are common among these patients. **Aims**: To evaluate the clinical manifestations and hematological parameters of β-thalassemia patients in Jazan, Saudi Arabia. **Settings and Design:** This is a cross-sectional study conducted in Jazan region, Saudi Arabia. **Methods and Materials:** We included 36 β-Thalassemia major patients who admitted to PMNH during the period from February 1, 2016 to December 31, 2017. Clinical features were obtained via physical examination. The hematological parameters were obtained from the patients' medical records. **Statistical Analysis Used:** Descriptive and inferential statistics were conducted using SPSS. Continuous data was evaluated using independent sample *t*-test and Chi-square was used to evaluate categorical variables. $P < 0.05$ indicated statistical significance. **Results:** Mean age was 18.56 ± 6.89 years. Males were 23 (63.9%). About 41.4% of patients were underweight. Exposing of the upper teeth was the most prominent feature ($n = 19$, 59.4%). The majority of patients were splenectomized (62.1%). About two-thirds have moderate anemia. More than half of the patients (58.8%) had high WBCs counts and 35.3% had a high platelet count, especially among those who underwent splenectomy. Approximately, two-thirds had a ferritin level higher than 2500 ng/ml. O^+ blood group was the most frequent blood group among the patients ($n = 15$, 46.9%). **Conclusions:** Deteriorated clinical and hematological parameters in our study justify the need for more efforts for regular evaluation and follow-up of the βTM patients and reevaluation of the management protocols to be improved or modified.

Keywords: β thalassemia, clinical, features, hematological, Jazan

Introduction

Beta-thalassemia is a hereditary blood disorder with an autosomal recessive pattern of inheritance.[1]

It has diverse clinical presentations and multiple complications.[1,2] Beta-thalassemia is one of the prevalent hereditary blood disorders in Saudi Arabia, especially in Jazan region. In comparison with healthy individuals, thalassemia patients have different hematological parameters such as low levels of erythrocytes and Hb and high ferritin levels.[3] A wide variety of health problems, including thalassemia, usually assessed first in the primary care centers.[4] This study was conducted with the aim of evaluation of the clinical manifestations and hematological parameters among βTM patients in Jazan, Saudi Arabia.

Subjects and Methods

This was a cross-sectional study conducted in the hematology center at PMNH in Jazan region of Saudi Arabia. The hematology center was established in 2016 and is where the majority of βTM patients in Jazan region currently receive

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treatment for the manifestations of their disease. βTM patients who regularly visited or were admitted to PMNH during the period from February 1, 2016 to December 31, 2017 were included in this study. Demographic data, including age, gender, and nationality, were obtained from the patients through interviews by medical interns who were working at PMNH. In addition, height, weight, and clinical features of thalassemia, including frontal bossing, prominent malar eminence, depressed bridge of the nose, overgrowth of the upper jaw (maxillary hypertrophy) causing exposure of the upper teeth, and spleen measurements were obtained thorough physical examinations. Ultrasound results and hematological parameters, including complete blood count (CBC), blood type, and serum ferritin levels, were obtained from the patients' medical records. Informed consent was obtained from all individual participants included in the study. The present study was approved by Jazan Institutional Review Board (IRB) with registry 1920 on July 30. Collected data were verified manually, entered into a personal computer, and analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 25 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics, including frequencies and percentages for categorical variables and mean (M) and standard deviation (SD) for continuous variables, were calculated for study variables. The Chi-square test was applied to compare categorical variables. An independent sample *t*-test was used in the comparison of mean values of different variables. Any two-sided *P* values less than 0.05 were considered statistically significant.

Results

Patients' characteristics

In total, 36 βTM patients were included in the study, with 23 males (63.9%) and 13 females (36.1%). During their admissions, the patients had physical examinations and their medical records were reviewed. The mean age of the participants was 18.56 years (SD = 6.894). Mean height and weight were 148.86 ± 11.202 cm and 40.46 ± 9.625 kg, respectively. Adult body mass index (BMI) was calculated using the formula weight (kg)/[height (m)]^2. For pediatric patients (<18 years), the percentile chart for BMI calculation was used. Normal BMI was found in 58.6% of patients, 41.4% of patients were underweight, and none of the patients was overweight. About two-thirds of the patients (62.1%) were splenectomized, while about 31% of the patients had splenomegaly, and only 6.9% of them had a normal spleen status.

Clinical features

Exposure of the upper teeth was the most common feature among βTM patients (*n* = 19; 59.4%), followed by maxillary hypertrophy (*n* = 17; 53.1%). Other features were less frequent, including prominence of the malar eminence (*n* = 5; 15.6%), frontal bossing (*n* = 4; 12.5%), and a depressed nasal bridge (*n* = 3; 9.4%). Further analysis revealed that there was a significant difference between males and females regarding exposure of the upper teeth ($P = 0.015$). However, other features did not significantly differ between the two groups [Table 1]. Patients who started blood transfusions at the age of one year or later were more likely to have maxillary hypertrophy ($P = 0.005$) and exposure of the upper teeth ($P = 0.031$) than were those who started blood transfusions within one year of age [Table 2].

Hematological parameters

Hb levels, together with other parameters, can determine anemia status of the patients. However, according to the World Health Organization (WHO), the classification of anemia severity depending on Hb level differs across different age groups. In this study, the mean value of Hb levels was 8.671 ± 1.554 g/dl. We found that 2.9% of the patients were nonanemic, 2.9% had mild anemia, 61.8% had moderate anemia, and 32.4% had severe anemia. The mean value of mean corpuscular volume (MCV) was 74.997 ± 5.513 fl. A low level of MCV was found in 79.4% of the patients, while the remaining 20.6% had normal MCV. The mean value of white blood cell (WBC) levels was 18.547 ± 15.443 × 10^3/μl. We found 58.8% of patients had abnormally high WBC levels, while 38.2% had normal WBC levels, and 2.9% had low WBC levels. The mean value of platelet counts was 378.56 ± 163.469/ml. Normal platelet counts were found in 64.7% of the patients, while the remaining (35.3%) had high platelet counts. The ferritin levels of 77.1% of patients were greater than 2500 ng/ml, while 17.1% had a level of 1000–2500 ng/ml, and 5.8% had a ferritin level less than or equal to 1000 ng/ml [Table 3]. The largest group of βTM patients were of the O^+ blood type (*n* = 15; 46.9%). The second-most frequent blood type was A^+ (*n* = 13; 40.6%), followed by blood types B^+ (*n* = 2; 6.3%), B^- (*n* = 1; 3.1%), and A^- (*n* = 1; 3.1%) [Table 4].

Table 1: Frequency of clinical thalassemic features among beta-thalassemia major (βTM) patients (*n*=27)

Feature	Male *n* (%)	Female *n* (%)	Total *n* (%)	*P*
Frontal Bossing				
Yes	4 (21.1%)	0 (0.0%)	4 (14.8%)	0.160
No	15 (78.9%)	8 (100.0%)	23 (85.2%)	
Prominent malar eminence				
Yes	5 (26.3%)	0 (0.0%)	5 (18.5%)	0.108
No	14 (73.7%)	8 (100.0%)	22 (81.5%)	
Overgrowth of the Upper Jaw (maxillary hypertrophy)				
Yes	14 (73.7%)	3 (37.5%)	17 (63.0%)	0.075
No	5 (26.3%)	5 (62.5%)	10 (37.0%)	
Exposure of the Upper Teeth				
Yes	16 (84.2%)	3 (37.5%)	19 (70.4%)	0.015
No	3 (15.8%)	5 (62.5%)	8 (29.6%)	
Depressed Nasal Bridge				
Yes	3 (15.8%)	0 (0.0%)	3 (11.1%)	0.233
No	16 (84.2%)	8 (100.0%)	24 (88.9%)	

P<0.05 is statistically significant

Table 2: Incidence of thalassemic features relative to age of starting blood transfusions

Feature		Transfusions started prior to one year of age *n* (%)	Transfusions started after one year of age *n* (%)	*P*
Frontal Bossing	Yes	0 (0.0%)	4 (17.4%)	0.366
	No	4 (100.0%)	19 (82.6%)	
Prominent Malar Eminence	Yes	0 (0.0%)	5 (21.7%)	0.302
	No	4 (100.0%)	18 (78.3%)	
Maxillary Hypertrophy	Yes	0 (0.0%)	17 (73.9%)	0.005
	No	4 (100.0%)	6 (26.1%)	
Exposure of the Upper Teeth	Yes	1 (25.0%)	18 (78.3%)	0.031
	No	3 (75.0%)	5 (21.7%)	
Depressed Nasal Bridge	Yes	0 (0.0%)	3 (13.0%)	0.444
	No	4 (100.0%)	20 (87.0%)	

P<0.05 is statistically significant

Table 3: Hematological evaluation of beta-thalassemia major (βTM) patients

	Male *n* (%)	Female *n* (%)	Total *n* (%)	*P**
Hb (g/dl) M±SD	8.58±1.60	8.82±1.53	8.67±1.55	0.522
Nonanemia	1 (4.8%)	0 (0.0%)	1 (2.9%)	
Mild anemia	0 (0.0%)	1 (7.7%)	1 (2.9%)	
Moderate anemia	13 (61.9%)	8 (61.5%)	21 (61.8%)	
Severe anemia	7 (33.3%)	4 (30.8%)	11 (32.4%)	
MCV (fl) M±SD	73.78±6.24	76.96±3.45	75.00±5.51	0.778
Normal	4 (19.0%)	3 (23.1%)	7 (20.6%)	
Low	17 (81.0%)	10 (76.9%)	27 (79.4%)	
WBC (10^3/μl) M±SD	20.14±17.28	15.97±12.12	18.55±15.44	0.591
Normal	7 (33.3%)	6 (46.2%)	13 (38.2%)	
High	13 (61.9%)	7 (53.8%)	20 (58.8%)	
Low	1 (4.8%)	0 (0.0%)	1 (2.9%)	
Platelets/ml M±SD	408.62±178.61	330.23±127.30	378.56±163.47	0.241
Normal	12 (57.1%)	10 (76.9%)	22 (64.7%)	
High	9 (42.9%)	3 (23.1%)	12 (35.3%)	
Ferritin (ng/ml) M±SD	4074.83±1981.76	3777.86±2010.32	3964.53±1968.07	0.693
≤1000	1 (4.5%)	1 (7.7%)	2 (5.8%)	
>1000-2500	3 (13.6%)	3 (23.1%)	6 (17.1%)	
>2500	18 (81.8%)	9 (69.2%)	27 (77.1%)	

*Chi square test for categorical variables. *P*<0.05 is statistically significant. M=mean, SD=standard deviation, Hb=hemoglobin, MCV=mean corpuscular volume, WBC=white blood cells

Comparison of hematological variables in splenectomized versus nonsplenectomized βTM patients

WBC and platelet levels for splenectomized βTM patients ($25.84 \pm 16.56 \times 10^3$/ul and 488.56 ± 145.90/ml, respectively) were significantly higher ($P = 0.006$) than those in nonsplenectomized βTM patients ($7.94 \pm 2.83 \times 10^3$/ul and 247.55 ± 65.60/ml, respectively). Other parameters were not significantly different between the two groups [Table 5].

Discussion

Primary prevention of hemoglobinopathies, including thalassemia, by population screening, premarital and antenatal diagnosis, and avoiding marriages between carriers is the most important role to avoid their complications.[5,6] In addition, primary care physicians have an important role in identifying patients at risk for or presenting with a clinically significant form of thalassemia, and to provide ongoing education and support to patients and their families.[7] Maxillofacial manifestations are prevalent among βTM patients.[8] These manifestations include frontal bossing, prominent malar bones, maxillary hypertrophy, a depressed nasal bridge, and exposure of the upper teeth.[8-11] In this study, frontal bossing was present in 14.8% of the βTM patients. This feature is attributed mainly to hyperactive bone marrow that leads to enlargement of the outlines of the flat bones of the skull, including the frontal bone. Higher prevalence rates of frontal bossing have been reported in other studies.[11,12] Similar pathophysiology causes malar bone prominence and maxillary hypertrophy. Malar bone prominence was observed in 18.5% of the βTM patients in this study. This percentage was lower than that found in a study (31.8%) conducted in Iran, 2017.[8] Although frontal bossing and malar bone prominence were less frequent in our study than in others, we found that maxillary hypertrophy was present in nearly 73.9% of those included in this study. This finding was similar to that of Girinath *et al.*, who found that it presents in 78% of βTM patients.[11] However, a lower prevalence (34%) was found in another study.[10]

The defect in all beta-globin chains in βTM affects Hb production within RBCs, which consequently leads to a lower

Table 4: Frequency of blood types of beta-thalassemia major (βTM) patients (*n*=32)

Blood type	Male	Female	Total	*P*
O+	10 (52.6%)	5 (38.5%)	15 (46.9%)	0.607
A+	6 (31.6%)	7 (53.8%)	13 (40.6%)	
A-	1 (5.3%)	0 (0.0%)	1 (3.1%)	
B+	1 (5.3%)	1 (7.7%)	2 (6.3%)	
B-	1 (5.3%)	0 (0.0%)	1 (3.1%)	

P<0.05 is statistically significant

Table 5: Hematological values in splenectomized versus nonsplenectomized β-thalassemia major (βTM) patients

Parameter	Splenectomized *n*=20	Nonsplenectomized *n*=9	*P*
Hb (g/dl) M±SD	9.04±1.66	8.44±1.33	0.408
MCV (fl) M±SD	76.57±4.84	74.04±3.09	0.178
WBC (10^3/μl) M±SD	25.84±16.56	7.94±0.83	0.006
PLT/ml M±SD	488.56±145.90	247.55±65.60	0.000
Ferritin (ng/ml) M±SD	4267.51±2100.86	3622.19±1918.29	0.656

P<0.05 is statistically significant. M=mean, SD=standard deviation, Hb=hemoglobin; MCV=mean corpuscular volume, WBCs=white blood cells, PLT=platelets

oxygen-carrying capacity. This abnormality results in microcytic hypochromic anemia and low MCV of the RBCs.[1,2] We classified patients according to WHO criteria as having mild, moderate, or severe anemia.[13] In this study, 61.8% of patients had moderate anemia and 32.4% had severe anemia. Low MCV was found in 79.4% of the βTM patients. In our study, microcytic hypochromic anemia was found in almost all βTM patients. These results are consistent with those of other studies, where Hb levels among βTM patients were lower than those of normal individuals.[14,15] and βTM patients were reported to have severe anemia[16] The anemic condition caused by βTM reduces the oxygen-carrying capacity of RBCs, creating excessive pressure on respiratory muscles. This causes a forceful pressure for breathing, with the wide opening of the nostrils and flaring of the alae, resulting in a depressed nasal bridge.[10] We found a lower prevalence of depressed nasal bridge (11.1%) than found in other studies (70%).[12,17]

Splenomegaly is known to occur in βTM patients and may cause abdominal enlargement and discomfort. Hypersplenism can occur, causing excessive destruction of RBCs. As a result, many βTM patients require splenectomy, which can improve their quality of life.[12,16] In our study, splenectomy was performed in 62.1% of the patients. Similar results were reported in other studies.[8,12] An increase in RBC destruction in the spleen of βTM patients eventually leads to decreases in RBC count, Hb, hematocrit, and RBC indices. Conversely, these hematological parameters would be expected to increase after splenectomy. In this study, Hb levels were higher among those who underwent splenectomy than among those who did not, but the difference did not reach a statistical significance. Similar results were found in other studies in which splenectomy was found to improve anemia but did not reduce the iron burden or the requirement for blood transfusions in various transfusion-dependent disorders.[18-20] The spleen plays an important role in the modulation of immunity, inflammation, and thrombosis. Many complications post-splenectomy may be expected. In this study, splenectomized patients had higher WBC counts than those of nonsplenectomized patients, similar to results reported in other studies.[18,19] The splenectomized patients also had higher levels of platelets than those of nonsplenectomized patients. This thrombocytosis is a complication well-known to occur after splenectomy as a consequence of continuing anemia with a hyperplastic marrow.[21,22] Venous thromboembolic events following splenectomy have been reported in many studies,[19,20,22] requiring an early diagnosis to start proper management.[23]

High levels of ferritin make patients prone to iron overload, which is the most frequent complication associated with repeated blood transfusions.[2] Iron overload is harmful to the body and can cause mortality because of iron accumulation in organs, including the heart, liver, and kidneys.[16] Although the patients in this study were on chelation therapy, the majority of them had a ferritin level higher than 2500 ng/ml (M = 3964.5 ± 1968 ng/ml). This result was similar to that in a study by Ikram *et al.* conducted in Pakistan, where the mean ferritin level in patients was 3390 + 135.6 ng/ml. They suggested that improper treatment with iron chelators and lack of infusion pump availability were the two main reasons for these high ferritin levels.[24] New trends in chelation therapy combined with better patient education and monitoring provide promise for decreasing the consequences of toxic iron accumulation in the body and increasing the quality of life of transfusion-dependent thalassemia patients.[25-27]

According to current guidelines, blood transfusion is the cornerstone for the management of βTM.[28] Therefore, data about the common blood types among βTM patients and support from the blood banks with sufficient amounts of blood of these types are of great importance.[29] In this study, O^+ was the most common blood type among the βTM patients, followed by A^+. Although this is the first study to assess blood types in βTM patients in Jazan region, the results were similar to many studies conducted in various areas. For example, in Iraq and Iran, the most common blood type among βTM patients was O^+, followed by A^+.[30,31] Two studies conducted in India also found that O^+ was the most frequent blood type. However, in that region, B^+ was the second-most frequent blood type.[29,32] Our results are obviously consistent with the findings of Sarhan *et al.* as he found that, in the southwest region of Saudi Arabia, the O^+ blood type was the most frequent, followed by A^+.[33] This study had some shortcomings. It was a cross-sectional survey and only patients admitted to PMNH included in the study. WBC usually increases after splenectomy. In addition, frequent blood transfusion is associated with high ferritin levels. However, illness or infection status was not determined among those with high WBC count, especially in splenectomized patients. Also, compliance with chelation therapy was not known among our participants. In conclusion, this is the first study conducted in Jazan region of Saudi Arabia to evaluate clinical manifestations and hematological parameters of βTM patients. The results showed how considerably the clinical and hematological

parameters among βTM thalassemia patients are affected. They justify the importance of reevaluation of management protocols for improvement or modification, with greater efforts in regular evaluation and follow-up of βTM patients. Future studies are needed to discover the causes of the specific medical conditions seen among βTM patients and finding solutions for these problems. We recommend the activation of educational and interventional systems directed toward the improvement of βTM patients' health status and management.

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Conflicts of interest

There are no conflicts of interest.

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