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β-Thalassemia Major: Clinical Manifestations, Diagnosis, and Therapeutic Approach: A Clinical Case Study

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ABSTRACT

Background: β-thalassemia is an inherited hemoglobinopathy characterized by reduced or absent synthesis of the β-globin chains, with a high prevalence in populations of Mediterranean descent and a wider global distribution. We report the clinical case of a pediatric female patient with transfusion-dependent β-thalassemia major from western Libya. Her older sibling had been diagnosed with β-thalassemia major and subsequently underwent allogeneic bone marrow transplantation; both parents were identified as heterozygous carriers of the β-thalassemia trait.

Case Report: An 11-year-old girl from western Libya was diagnosed with homozygous β-thalassemia major, a genetic predisposition supported by confirmed parental carrier status. Owing to chronic anemia and ineffective erythropoiesis, the patient requires regular monthly red blood cell transfusions to maintain hematologic stability. Although allogeneic hematopoietic stem cell transplantation represents the only potentially curative intervention, its suitability is constrained by patient age, donor availability, comorbid conditions, and additional clinical factors.

Discussion: This report delineates the clinical and laboratory characteristics of β-thalassemia major in a patient from western Libya and summarizes the molecular pathogenesis of the disorder. β-thalassemia results from pathogenic variants in the β-globin gene (HBB) located on chromosome 11. Such mutations—including single-nucleotide substitutions, insertions, or deletions—reduce (β^{+}) or completely abolish (β^{0}) β-globin production, leading to diminished β-globin synthesis and consequent imbalance in hemoglobin assembly. Clinical manifestations typically emerge during childhood in individuals who inherit pathogenic variants from both carrier parents; in the present case, the patient's genotype is consistent with homozygous β-thalassemia major.

Conclusion: We discuss the hematologic and biochemical phenotype of this case and address the principal long-term complications of chronic transfusion therapy, particularly secondary iron overload and increased susceptibility to viral infections affecting both hepatic and extrahepatic sites. Finally, we review contemporary therapeutic approaches for β-thalassemia major and evaluate the potential utility of hematopoietic stem cell transplantation as a curative strategy for this patient.

KEYWORDS: thalassemia major; Hemoglobin electrophoresis; red blood cell transfusion; Iron overload; Allogeneic stem cell transplantation.

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INTRODUCTION

β-thalassemia major is one of the most significant autosomal recessive hemoglobin disorders in the Mediterranean basin, including Libya. The prevalence of the β-thalassemia trait is notably high, primarily due to historical selective pressures consistent with the malaria hypothesis. This hypothesis suggests that heterozygous carriers have a survival advantage against Plasmodium falciparum (1,2). Libya, located at a geographical and genetic intersection among Western Africa, Egypt, and Sub-Saharan Africa, exhibits a complex range of β-thalassemia mutations (3,4). Several studies have identified various mutations within the Libyan population, with IVS-I-110 (G→A), IVS-I-1 (G→A), and codon 39 (C→T) being among the most common (5,6). These mutations reflect the diverse ancestral lineages present in the country (7,8). Despite national screening efforts, the incidence of new cases remains a significant public health challenge, exacerbated by high rates of consanguineous marriages that increase the likelihood of homozygous offspring (9,10).

β-thalassemia major is a severe autosomal recessive hemoglobinopathy characterized by a significant reduction or complete absence of β-globin chain synthesis (11). This defect disrupts the balance between α- and β-globin chains, resulting in ineffective erythropoiesis and chronic hemolytic anemia, which necessitates lifelong regular blood transfusions (12). Clinically, without adequate treatment, symptoms typically emerge as early as 6 to 24 months of age (13,14). These include growth retardation, severe hemolytic anemia, fever, abdominal pain, delayed development, and bone abnormalities, which can lead to mortality in severe cases (15). Pathophysiologically, secondary iron overload complicates β-thalassemia major due to recurrent transfusions and increased gastrointestinal iron absorption. If left untreated, iron overload can lead to multi-organ failure, particularly affecting the myocardium, liver, and endocrine system (16).

Thalassemia is a hereditary autosomal recessive blood disorder that is distinctly categorized into two main types: alpha thalassemia and β-thalassemia, based on mutations in the hemoglobin alpha or β-chains. Major β-thalassemia arises from mutations in both alleles of the β-chain genes, leading to significant health challenges. When only one β-chain gene is mutated, patients may present with intermediate or minor β-thalassemia, with the impact of the condition varying accordingly. The key diagnostic tests, including a Complete Blood Count (CBC) and High-Performance Liquid Chromatography (HPLC), are essential for accurately assessing the condition (17,18). The CBC evaluates hemoglobin (Hb), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH), while HPLC provides insight into the levels of various hemoglobin types, such as HbA (adult hemoglobin, $\alpha_2\beta_2$), HbA_2 (hemoglobin subtype, $\alpha_2\delta_2$), and HbF (fetal hemoglobin, $\alpha_2\gamma_2$) (19). Deviations in these measurements clearly indicate the severity of thalassemia, which can range from minor to major forms. According to the Thalassemia International Federation, regular blood transfusions every 2 to 3 weeks are crucial for maintaining a normal hemoglobin level (approximately 8 g/dL), which is vital for the proper growth and development of children up to ages 10 to 12 (20,21). Furthermore, life expectancy for patients can significantly improve through interventions such as bone marrow or hematopoietic stem cell transplantation. Immediate and consistent medical attention is essential for managing this condition effectively.

The management of β-thalassemia major in Libya has evolved significantly, although it is still affected by socio-economic factors treatment guidelines recommend maintaining pre-transfusion hemoglobin levels between 9.5 and 10.5 g/dL (22). This target helps to reduce excessive expansion of the erythroid marrow and prevents skeletal deformities. However, and logistical challenges that are crucial for providing consistent care. Established the resultant iron loading necessitates chelation therapy with agents such as deferoxamine (DFO), deferiprone (DFP), or deferasirox (DFX) (23). Recent clinical observations indicate emerging complications in the aging thalassemia major population, including renal tubular dysfunction and hypercalciuria, which are frequently associated with prolonged use of certain oral chelators, notably DFX. In addition, the psychosocial burden on Libyan patients is substantial; the chronicity of the disease often leads to social isolation, heightened anxiety, and diminished quality of life, underscoring the need for a holistic biopsychosocial approach to management.

Recently, novel techniques have become available in developed countries, such as erythropoiesis modification strategies, gene therapy, and gene editing technologies using editing tools such as zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeats (CRISPR) along with CRISPR-associated nuclease 9 (CRISPR-Cas9) (24,25).

This case study aims to delineate the clinical course, molecular diagnosis, and therapeutic challenges encountered by a Libyan

patient with β-thalassemia major, thereby providing a framework for optimizing care in resource-constrained settings.

Clinical Case Report

An 11-year-old girl with β-thalassemia major, confirmed by genetic testing, was initially thought to have a phenotype consistent with β-thalassemia intermedia. She was first diagnosed at age 7 and resided in the western region of Libya. At that time, her hemoglobin level was 8.5 g/dL, prompting further evaluation with hemoglobin electrophoresis, which ultimately confirmed the diagnosis of β-thalassemia major.

In 2018, she received packed red blood cell transfusions, and her requirement increased over the past 2 years to every two weeks. In March 2019, she was started on hydroxyurea for six months and was also taking Exjade (500 mg) and folic acid (5 mg) daily. By March 2020, she reported no complaints, though a physical examination revealed signs consistent with thalassemia features, notably marked splenomegaly on abdominal examination.

In 2020, the child was evaluated for the possibility of stem cell transplantation at the Medical University Hospital. A comprehensive assessment, including hematological, biochemical, and viral screenings, was performed. Her parents had a strong history of β-thalassemia minor, and her eldest sister had β-thalassemia major and had undergone a bone marrow transplant in 2006. The CBC and blood indices are illustrated in Table 1, and the results of hemoglobin electrophoresis in the family are shown in Table 2.

This case is a retrospective case study from the Medical University Hospital, and written consent was obtained from her father for publication as a strictly confidential case.

Table 1: CBC Parameters

CBC Parameter	Female Patient	Sister*	Mother	Father	Reference Range
Hemoglobin (g/dL)	8.9	9.6	11.1	12.3	12 – 17
RBC ($\times 10^{12}$/L)	3.1	—	—	—	—
MCV (fL)	71.0	84.2	—	—	75 – 85
MCH (pg/cell)	24	24.9	—	—	26 – 32
MCHC (g/dL)	34	29.5	—	—	32 – 36
RDW-CV (%)	25.4	—	—	—	9.9 – 15.5
WBC ($\times 10^3$/µL)	10.54	37.6	—	—	50 – 70
Platelets ($\times 10^3$/µL)	315	802	—	—	20 – 40
Ferritin (ng/mL)	885.8	—	—	—	30 – 200

MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW-CV: red cell distribution width-coefficient of variation; WBC: white blood cells.

** Her sibling had a post-bone marrow transplant for β-thalassemia major.*

Table 2: HPLC Analysis

HPLC Parameter	Female Patient	Sister*	Mother	Father	Reference Range
HbA (%)	0	94	94.1	94.3	94.3 – 98.5
HbF (%)	98.2	3.5	0.8	0.4	0.2 – 2.0
HbA_2 (%)	1.8	2.5	5.1	5.3	2% – 3.4
RBC Appearance	Microcytic, hypochromic			Normocytic, normochromic	

*A: adult; F: fetal; A_2: hemoglobin subtype A_2; HPLC: High-Performance Liquid Chromatography. * This case had a post-bone marrow transplant for β-thalassemia major*

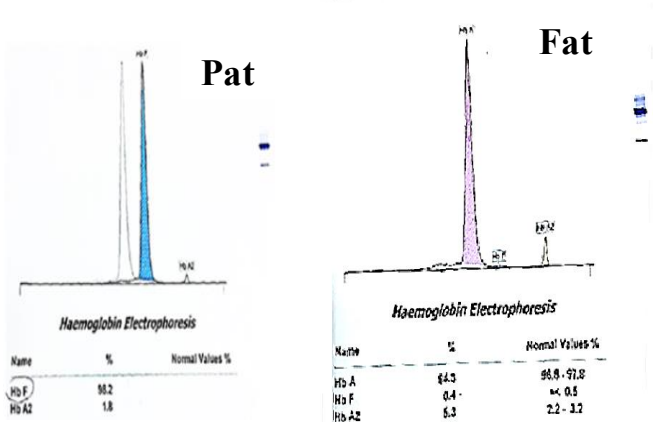

Figure 1: presents the hemoglobin electrophoresis results for the affected female child and her father.

Viral Screening

In the context of chronic transfusion therapy, the patient underwent a targeted screening for blood-borne viral infections. In 2020, a serologic survey evaluated Hepatitis B virus (HBV), Hepatitis C virus (HCV), and Human Immunodeficiency Virus (HIV), with all results remaining negative as demonstrated in Table 3. In contrast, a serological survey demonstrated positive IgG antibodies for Cytomegalovirus (CMV), Varicella-Zoster Virus (VZV), and Epstein-Barr Virus (EBV). These findings align with the heightened susceptibility to viral infections observed in individuals with β-thalassemia major, attributable to repeated transfusion exposure, iron overload, and an underlying immune disturbance (26).

Table 3: Viral Screening Survey for the Patient

Screen for Viral Hepatitis	Results	Screening for Other Viruses	Results
HBc Ab	Negative	CMV IgM	Negative
HBsAg	Negative	CMV IgG	**Positive**
HCV	Negative	HSV 1 & 2 IgM	Negative
HIV	Negative	HSV 1 & 2 IgG	Negative
		VZV IgM	Negative
		VZV IgG	**Positive**
		EBV IgM	Negative
		EBV IgG	**Positive**

HBc Ab: Hepatitis B core antibody; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; HIV: Human Immunodeficiency Virus; CMV: Cytomegalovirus; HSV: Herpes Simplex Virus; VZV: Varicella-Zoster Virus; EBV: Epstein-Barr Virus.

Biochemical Analysis

Overall, most biochemical parameters fell within the established reference ranges. Notable exceptions included decreased hemoglobin concentration and elevated serum transferrin levels, findings that are consistent with iron overload. In addition, vitamin D_3 deficiency was detected and subsequently managed with oral vitamin D supplementation. Furthermore, increased total, direct, and indirect bilirubin levels were observed, as reported in Table 4. Thyroid function, assessed by free T_4 and TSH, remained within normal limits. This clinical study involved an 11-year-old female. Although hypothyroidism is more commonly identified during the second decade of life, it has been proposed to be associated with iron overload in patients with β-thalassemia major. Elevated activated Partial Thromboplastin Time (aPTT), prothrombin time, and INR were also documented, and these abnormalities are largely attributable to iron overload and/or hypersplenism.

Molecular Genetic Analysis

An EDTA-anticoagulated blood sample was submitted for β-globin gene mutation testing, targeting 22 common β-thalassemia mutations prevalent in the Mediterranean

population. Mutation analysis was conducted using selective mutation PCR followed by a reverse hybridization assay. The patient was found to carry the IVS 1.1 [G>A] mutation

Table 4: Initial Laboratory Investigations

Parameter	Value	Reference Range
Hemoglobin (g/dL)	8.9	12–17
Ferritin (ng/mL)	885.8	30–300
Iron (ng/dL)	113	50–170
Alkaline Phosphatase (U/L)	415	Child < 727
Alanine Aminotransferase (ALT) (U/L)	13	7–50
Aspartate Aminotransferase (AST) (U/L)	6	8–48
Gamma Glutamyl Transferase (γGT) (U/L)	19	7.0–32
Total Bilirubin (mg/dL)	2.4	0.2–1.2
Direct Bilirubin (mg/dL)	0.3	0–0.3
Indirect Bilirubin (mg/dL)	2.1	0.2–0.8
Prothrombin Time (sec)	16	12–13.5
INR (%)	1.2	0.8–1.1
aPTT (sec)	40.5	35–38
Total Protein (g/dL)	7.8	6.4–8.2
Albumin (g/dL)	4.1	3.4–5.0
Serum Calcium (mg/dL)	8.9	8.7–10.7
Vitamin D_3 (ng/mL)	12.35	≥ 30
Parathyroid Hormone (pg/mL)	52.2	15–68
HbA_{1c} (%)	< 4	< 5.7
TSH (mIU/mL)	3.9	0.6–4.84
Free T_4 (ng/dL)	1.28	0.8-2.1

INR: International Normalized Ratio; aPTT: activated Partial Thromboplastin Time; TSH: Thyroid Stimulating Hormone; T_4: Thyroxine.

Radiological Imaging

Multiple imaging techniques were employed to assess the condition. Liver iron concentration was quantified to guide decisions regarding blood transfusion and to determine the need for iron-chelating therapy. In addition, a computed tomography (CT) examination of the maxillary sinuses demonstrated secondary obliteration of both maxillary sinuses, attributed to increased intramedullary expansion. Skeletal involvement was evaluated using dual-energy X-ray absorptiometry (DEXA), with bone mineral density (BMD) measured at the anteroposterior (AP) lumbar spine segments (L1–L4). The obtained age-adjusted Z-score fell within the expected normal range (Z = −1.3) for the pediatric patient.

MRI of the Abdomen for Liver Iron Quantification

Liver iron concentration (LIC) was measured using the hepatic R2 MRI technique (FerriScan). The LIC was determined to be 4.56 mg/g of dry liver tissue, consistent with mild hepatic iron overload.

Conclusion

In conclusion, the patient's hemoglobin level remained suboptimal until hemoglobin electrophoresis and genetic testing confirmed β-thalassemia major, despite clinical features suggesting an intermediate phenotype. Longitudinal follow-up demonstrated progressively increasing transfusion requirements and the development of clinically significant splenomegaly, which persisted despite treatment with hydroxyurea, iron chelation (Exjade), and folic acid, thereby prompting a pre-transplant assessment. Magnetic resonance imaging showed mild liver iron overload (MRI LIC 4.56 mg/g) alongside radiologic findings consistent with typical skeletal involvement; however, DEXA results were age-appropriate. Notably, the patient underwent splenectomy and received appropriate post-splenectomy vaccinations. Following splenectomy, her transfusion requirements decreased substantially. While the family history underscores the central contribution of genetic factors to disease management, hematopoietic stem cell transplantation is not currently indicated. This option will be reconsidered only if clinical status deteriorates, particularly in the event of renewed escalation in transfusion needs, which are presently stable.

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