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Beyond genetics: Hypertriglyceridemia in the realm of thalassemia – A case report

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Abstract

Beta-thalassemia major, a severe hereditary hemolytic anemia, is typically associated with a normal serum lipid profile. However, rare cases suggest an idiopathic association with hypertriglyceridemia, termed Hypertriglyceridemia–Thalassemia Syndrome. We report a 6-month-old male infant with beta-thalassemia major and severe hypertriglyceridemia (triglyceride level: 1994 mg/dL). Following blood transfusions and dietary modifications, triglyceride levels decreased significantly to 619 mg/dL, suggesting a self-limiting mechanism. This case underscores the importance of screening for hypertriglyceridemia in thalassemia patients to mitigate associated risks, such as atherosclerosis and thromboembolism.

Keywords: Beta-thalassemia major, Hypertriglyceridemia, Hypertriglyceridemia-thalassemia syndrome

1. Introduction

Thalassemia encompasses a group of genetic disorders characterized by impaired globin chain synthesis, resulting in an imbalance between alpha- and beta-globin production.[1] Beta-thalassemia major, a severe form of transfusion-dependent thalassemia, arises from mutations in the beta-globin gene, leading to reduced (β^+) or absent (β^0) beta-globin production.[2] This causes ineffective erythropoiesis, severe anemia, and clinical manifestations such as pallor, hepatosplenomegaly, and failure to thrive.[3]

1.2. Hypertriglyceridemia

Hypertriglyceridemia, defined as elevated serum triglyceride levels, is uncommon in beta-thalassemia major. When present, it may predispose patients to thromboembolism and atherosclerosis, increasing morbidity.[4,5] The rare association, known as Hypertriglyceridemia–Thalassemia Syndrome, has been sporadically reported, particularly in the Indian subcontinent.[6,7] This case report describes a 6-month-old infant with beta-thalassemia major and severe hypertriglyceridemia, highlighting its clinical implications and management.

2. Case report

A 6-month-old male infant, born to non-consanguineous parents, was admitted to the pediatric intensive care unit with a 3-month history of failure to thrive, 1-month history of hair loss, and excessive irritability. Born at term via normal vaginal delivery with a birth weight of 2.5 kg, the infant was exclusively breastfed and had received all age-appropriate vaccinations. There were no perinatal complications.

On examination, the infant exhibited severe pallor, tachypnea, tachycardia, and hepatosplenomegaly (liver span: 7.5 cm), suggestive of congestive cardiac failure. Anthropometric measurements revealed a weight of 5.5 kg [<-3 Standard Deviation (<-3SD)], length of 64 cm (−2 SD–−1 SD), and head circumference of 40.5 cm (−2 SD–−1 SD). No edema, lymphadenopathy, ascites, or bleeding tendencies were noted.

Laboratory investigations included a complete blood count (CBC), C-reactive protein, liver and renal function tests, peripheral smear analysis, and lipid profile. The CBC revealed:

- White blood cells: 21 × 10^3/μL
- Red blood cells: 1.73 million/μL
- Hemoglobin: 6.4 g/dL

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- Hematocrit: 10%
- Mean corpuscular volume (MCV): 57.6 fL
- Mean corpuscular hemoglobin: 36.8 pg
- Mean corpuscular hemoglobin concentration: 63.9 g/dL
- Platelet count: 597 × 10^3/μL

Peripheral smear showed marked anisopoikilocytosis, microcytic hypochromia, teardrop cells, target cells, ring cells, polychromatic cells, and nucleated red blood cells. The serum was grossly lipemic, and the lipid profile revealed severe hypertriglyceridemia (triglycerides: 1994 mg/dL). High-performance liquid chromatography (HPLC) was attempted but rejected due to lipemia. Vitamin B12 levels were normal. Ophthalmologic examination indicated Grade 1 lipemia retinalis.

Management included broad-spectrum antibiotics, blood transfusion, and dietary modifications incorporating medium-chain triglyceride (MCT) oil and omega-3 fatty acids. After four blood transfusions, triglyceride levels decreased to 619 mg/dL. Whole-exome sequencing confirmed compound heterozygous pathogenic variants in the *HBB* gene, establishing a diagnosis of beta-thalassemia major. Parental HPLC analysis confirmed both parents as carriers of beta-thalassemia minor. Repeat HPLC post-transfusion revealed elevated HbF and HbA2 levels, consistent with the patient's age and diagnosis. An incidental finding of a likely pathogenic variant in the *PEPD* gene (associated with prolidase deficiency) was deemed unrelated to the primary condition. Parental consent was obtained for this report.

3. Discussion

Beta-thalassemia major typically manifests within the 1st year of life with severe hemolytic anemia, pallor, hepatosplenomegaly, and growth failure.[2] It results from mutations in the beta-globin gene on chromosome 11, causing absent or reduced beta-globin production.[1] Hemoglobin F predominates, with absent hemoglobin A. In India, approximately 10% of global thalassemia cases are reported annually, underscoring its public health significance.[1]

Hypertriglyceridemia in beta-thalassemia major, termed Hypertriglyceridemia–Thalassemia Syndrome, is rare and poorly understood.[4-6] Affected patients, typically presenting between 5 months and 2 years of age, exhibit elevated triglyceride levels without primary lipid disorders or secondary causes such as diabetes or hypothyroidism.[5,6] In this case, the 6-month-old infant presented with severe hypertriglyceridemia, which resolved significantly following transfusions and dietary modifications. This aligns with prior reports suggesting a self-limiting mechanism.[4,7]

The pathophysiology of this association remains unclear but may involve altered lipid metabolism secondary to hemolytic stress or ineffective erythropoiesis.[3,5] Hypertriglyceridemia increases the risk of atherosclerosis, thromboembolism, and acute pancreatitis, necessitating early recognition.[4,6] Parental lipid profiles were normal, and no clinical features of primary hypertriglyceridemia (e.g., xanthomas) were observed, supporting a thalassemia-related etiology.[7]

4. Hypertriglyceridemia-associated thalassemia major

Severe hypertriglyceridemia is an uncommon finding in infants with beta-thalassemia major and is sometimes described as Hypertriglyceridemia–Thalassemia Syndrome.[4-7] Similar presentation of thalassemia-associated metabolic disturbance, including hypertriglyceridemia, has been observed across various centers in India, including only five cases reported in Delhi, two in Kerala, one in Maharashtra, and around 12 cases, the maximum reported in Kolkata,[7] establishing the rarity of this association. Although the exact cause of this association is unclear, it is crucial to identify this condition to optimize the diagnosis and treatment of affected infants, especially in regions with low disease prevalence. In published cases, children typically presented between 5 months and 2 years of age. In this case, the infant presented at 6 months old. Investigations revealed normal lipid profiles in the parents, with no signs of associated conditions such as tonsillar hypertrophy, corneal arcus, tendon xanthomas, or tuberous xanthomas, ruling out primary hypertriglyceridemia. Secondary causes of hypertriglyceridemia were excluded based on clinical history and investigations.

5. Clinical implications

This case highlights the need to screen for hypertriglyceridemia in patients with beta-thalassemia major, particularly in regions with high disease prevalence.[5-7] Elevated triglycerides may contribute to early atherosclerosis and cardiovascular morbidity.[4-6] While spontaneous resolution is possible, regular lipid monitoring is essential to prevent complications.[3,7] Transfusion therapy and dietary interventions, such as low-fat diets and MCT oil supplementation, effectively reduced triglyceride levels in this patient, consistent with previous reports.

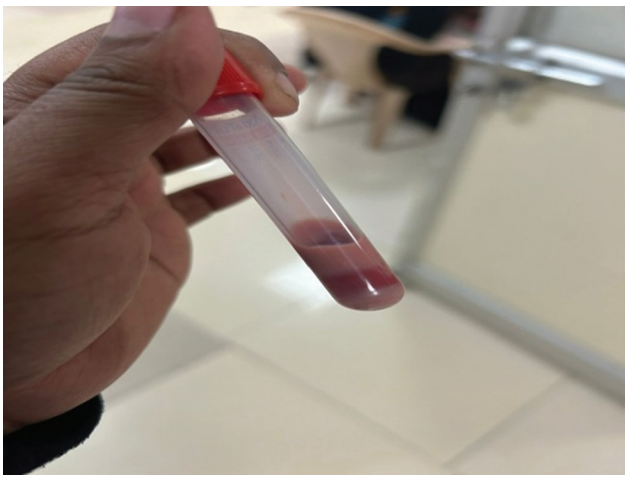
6. Conclusion

Hypertriglyceridemia-thalassemia syndrome is a rare but significant complication of beta-thalassemia major. Routine lipid screening in thalassemia patients can facilitate early diagnosis and management, reducing the risk of atherosclerosis, thromboembolism, and pancreatitis. Management typically involves transfusion therapy and dietary modifications, with regular follow-up to monitor lipid profiles and secondary complications. Recognizing this association, particularly in low-prevalence regions, ensures timely intervention and improved outcomes.

BIOCHEMISTRY

TEST	RESULT	UNITS	BIOLOGICAL REFERENCE RANGE
LIPID PROFILE			
TOTAL CHOLESTEROL	: 235	mg/dL	<200
TRIGLCERIDES(TG)	: 1994	mg/dL	<150
HDL CHOLESTEROL	: 187	mg/dL	<40-Low,>60-High
LDL CHOLESTEROL	: 93	mg/dL	<130
LDL/HDL Ratio	: 2.01		
CHOL/HDL Ratio	: 1.26		
HDL/LDL Cholesterol Ratio	: 0.50		

METHOD:-
Cholestrol Total- CHOD-POD Method
Triglyceride- GPO-POD Method
LDL/HDL - Direct Method.
VLDL- Calculated
TEST DESCRIPTION:-
Therapeutic target levels of lipids as per NCEP-ATP iii recommendations:
Total Cholesterol (mg/dL)200-Desirable,200-239-Borderline high,>240-High.
HDL Cholesterol(mg/dL),40-Low,>60-High.
LDL Cholesterol(mg/dL)100 Optimal ,[Primary Target of Therapy],100-129-near optimal/above optimal.
130-159-Borderline high,160-189High,>190 Very high.
Serum Triglycerides (mg/dL)150 Normal,150-199 Borderline high,200-499 High,>500 Very high.
NCEP recommends lowering of LDL Cholesterol as the primary therapeutic target with lipid lowering agents,
however,if triglycerides remain >200 mg/dL after LDL goal is reached ,set secondary goal for
non-HDL cholesterol(total minus HDL)30 mg/dL higher than LDL goal.



Chromatogram Report

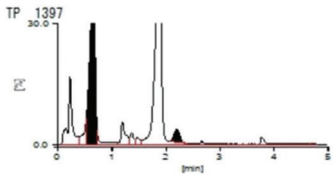
TOSOH G11 2025-01-19 15:29:23
ID 13748545
Sample No. 2025011915270031 SL 0002 - 05
Patient ID
Name
Comment

CALIB F Y =1.1773X + 0.6860
A2 Y =1.3719X + 0.1732

Name	%	Time	Area
F	38.7	0.66	503.34
A0	43.9	1.87	684.33
A2	3.9	2.21	41.01
E+			
D+			
S+			
C+			

Total Area 1558.75

HbF 38.7 % HbA2 3.9 %



[Unknown Peak]

Name	%	Time	Area
P00	9.7	0.23	150.58
P01	2.3	0.41	35.39
P02	1.4	0.73	21.86
P03	3.3	1.20	52.22
P04	1.4	1.37	22.13
P05	1.0	1.48	16.29
P09	1.3	3.80	20.41

Patient HPLC Report

MedGenome Labs Ltd.
Sy. Nos. 94/1C and 94/2, Tower 1, Ground Floor, Veerasandra Village, Attibele Hobli, Electronic City Phase-1, Electronics City, Bangalore, Bangalore South, Karnataka, India, 560100.
Tel : 1800 296 9696, Web: www.medgenome.com

MEDGENOME

DNA TEST REPORT - MEDGENOME LABS

Full Name / Ref No:	**SHIVA**	Order ID/Sample ID:	**1181677/8921353**
Gender:	Male	Sample Type:	Blood
Date of Birth / Age:	5 months		
Referring Clinician:	Dr. Priyanka Shrivastava, JK Hospital, Bhopal		
Test Requested:	**[SBZ_A] Whole Exome Sequencing (WES) (BPL Subsidised test)**		

CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

Baby *Shiva*, born of a non-consanguineous marriage, presented with clinical indications of anemia. Laboratory tests were suggestive of Hemoglobin 6.4 gm/dL. Lipid profile showed high triglyceride. Ophthal examination showed Lipemia Retinalis. There is a history of one blood transfusion done. He is suspected to be affected with Dyslipidemia (LPL deficiency) with Hemolytic anemia and has been evaluated for pathogenic variations.

RESULTS

COMPOUND HETEROZYGOUS VARIANTS CAUSATIVE OF THE REPORTED PHENOTYPE WERE DETECTED

SNV(s)/INDELS

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
HBB **(-)** (ENST00000335295.4)	Intron 1	c.92+5G>C **(5' Splice variant)**	Compound Heterozygous	Beta Thalassemia (OMIM#613985)	Autosomal recessive	Pathogenic **(PS3, PS4)**
	Exon 1	c.47G>A **(p.Trp16Ter)**				Pathogenic **(PVS1, PP5)**

Reclassification of these variants could be considered based on parental testing.

COPY NUMBER VARIANTS CNV(s)

No significant CNVs for the given clinical indications that warrants to be reported was detected.

VARIANT INTERPRETATION AND CLINICAL CORRELATION

VARIANTS 1 AND 2 (*HBB* gene):

Variant description: A compound heterozygous variant was detected in the ***HBB*** gene (Table).

Variant 1: A heterozygous 5' splice site proximal variant in intron 1 of the ***HBB*** gene (**chr11:g.5226925C>G; Depth: 161x**) that affects the position 5 nucleotides downstream of exon 1 (**c.92+5G>C**; **ENST00000335295.4**) was detected (Table).

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Name/Sample ID: Shiva/8921353

CAP ACCREDITED

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