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Case Series

CASE SERIES ON HEMOGLOBIN E-BETA-THALASSEMIA MAJOR

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ABSTRACT

Aim : The aim of case series is to describe the 3 Hemoglobin E β-thalassemia cases, which are unique and requires special care and attention to diagnose/manage.Its natural history is little known, and also the reasons for their clinical diversity, or/and its management.

Presentation of case : 3 cases of transfusion dependent Hemoglobin E β –thalassemia major were included in the study. The patients reported similar complaints of weakness and delayed milestones. The patients were on regular red blood cell transfusion and iron chelation therapy from the age of 3 years. The beta-globin gene defects were defined in all the cases using similar techniques. Thalassemia mutation analysis by reverse clot blot testing showed a compound heterozygous for IVS 1-5 [G-C] and codon 26 [G-A] beta E mutation in the beta globin gene. Evaluation for iron overload showed severe cardiac iron deposit and severe hepatic iron deposit on MRI T2. During hospital stay, the patients received antibiotics and immune-suppressants in common.

Discussion & Conclusion : Patients are treated by lifelong blood transfusion every 15 to 30 days along with iron chelation therapy. Repetitive transfusions cause iron overload, with life-threatening complications, like such as cardiomyopathy, endocrine disorders, liver failures and, ultimately, premature death.Awareness, education and screening play the most important part in the prevention of life-threatening complications and control of thalassemia.

Key words : *Hb E/β Thalassemia, Transfusion dependent, Hb E mutation, Thalassemia major*

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1. INTRODUCTION

The β-thalassemia is an inherited blood disorder resulting in the synthesis of little or no β-globin chains of hemoglobin.[1] Haemoglobin E-beta thalassemia (Hb E- β-thalassemia) genotype is responsible for almost one-half of all severe beta-thalassemia worldwide. This blood disorder characterized by marked clinical variability from asymptomatic anemia to a life-threatening disorder, which requires blood transfusions from infancy life.

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Hemoglobin E (HbE) is variant hemoglobin with a mutation in beta globin gene, which causes substitution of glutamic acid at position 26 for lysine in beta globin chain.

HbE disease generally presents in 3 forms namely Heterozygous (Genotype AE or HbE trait), Homozygous (Genotype EE or Hb E disease) and Compound Heterozygous[Hb E Beta Thalassemia (E β Thalassemia) & Sickle Cell / HbEdisease (SE Genotype)] states. [2]

Haemoglobin E β-thalassemia is the most common monogenic disorderin the Indian subcontinent. The average incidence of β-thalassemia heterozygotes in India is about 4%, and about8,000-10,000 children with major disease are born annually. This contributes to about 10% of the total thalasse-micinfants born all over the world [1].

Identification of this Hb variant thalassemia is very important, because doubly heterozygous state for HbE-β-thalassemia is characterized clinically by thalassemia major. The clinical manifestations of E-beta thalassemia generally include refractoryanemia, unexplained jaundice, splenomegaly, delayed puberty and stunted growth. In addition these patients may have complications like iron overload, hypercoagulable states particularly (post-splenectomy), and cardiopulmonary diseases. Thus the affected individual may besymptomatic and transfusion dependent at an early age.[3]

However, repetitive transfusions cause iron overload, with life-threatening complications like cardiomyopathy, endocrine dysfunction, liver diseases and, ultimately, premature death. In the lack of red blood cell transfusion, patients with beta-thalassemia major die within the first five years of life. Beyond the age of 35 years, only 50–65% of patients live with transfusions in high-income countries[3].It is very important to monitor the growth, quality of life, pubertal development, symptoms and signs of anemiain addition to regimen of regular transfusion[4].

The long-term clinical data and the phenotypic variability are the challenges for providing clinical recommendations in the management of patients. Recent research understanding reveals that, HbE thalassemia phenotype may be unstable, which may reflect changes in adaptation to anemia and possibly due to attenuation of the erythropoietin response over time. This factor may make it difficult for the development of broad treatment guidelines[5].

The Prognosis for individuals with this disease has been improved substantially in the recent decade with advances in blood transfusion, iron chelation therapy and transplantation of bone marrow. However, iron overload is the main cause for death amongst this population[6].

PRESENTATION OF CASES

In this study, 3 cases of Hb E β –thalassemia major have been included that were reported to the haematology department of the hospital during time period of two months. The inclusion criteria were children below 17 years of age with the diagnosis of transfusion dependent Hb E β –thalassemia major. All the 3 patients belonged to West Bengal, India.

The patients reported similar complaints of weakness and delayed milestones. One of them was currently admitted for elective splenectomy and the other two for bone marrow transplantation. The donor was full 10/10 match. One patient was symptomatic from the age of 2.5 years while the other two from the age of 3 years. Since then, they were receiving red blood cell transfusion and iron chelation therapy. The characteristics of the patients are discussed in Table 1.

Table 1: Characteristics of the patients:

Characteristics	Patient 1	Patient 2	Patient 3
Age (yrs), Gender	8, Female	9, Male	16, Male
Severity of anemia	Severe	Severe	Severe
Hepatosplenomegaly	+	+	+
Thalassemic face	+	+	+
Past medical/medication history	K/C/O (Known case of) E beta thalassemia	K/C/O E beta thalassemia	K/C/O E beta thalassemia. H/O Subclinical hypothyroidism, hypogonadism. On Tab. Hydroxyurea 500 mg OD (6/7)
History of blood transfusion	Since 3 years of age. 2 transfusions per month.	Since 3 years of age. 2 transfusions per month.	Since 3 years of age. 2 transfusions per month.
History of Chelation therapy	Tab. Asunra 500 mg OD	Tab. Desirox 500 mg OD	Initially on Tab. Kelfar 500 mg OD, later on Tab. Desirox 500 mg OD
Family history	Nil	Nil	Elder brother diagnosed with thalassemia along with him, he expired at the age of 10 years.
Abnormal laboratory values	Elevated reticulocyte count (6.46%) Reduced WBC count (100 cell/cu.mm) Reduced neutrophil (10%) Elevated total bilirubin (1.7 mg/dl)	Elevated total bilirubin (2.8 mg/dl)	Elevated total bilirubin (2.5 mg/dl)

On physical examination, the patients had hemolytic faces. Systemic examination of CVS, CNS, RS (respiratory system) and P/A (Pelvic / abdomen) showed no abnormalities. The 16-year-old patient had poor muscular development and absent secondary sexual characters.

For the patients 1 and 2, liver biopsy showed grade 4 iron overload with portal and periportal fibrosis. They were classified as Lucarelli class 3 and posted for transplantation.

The beta-globin gene defects were defined in all the cases using similar techniques. Thalassemia mutation analysis by reverse clot blot testing showed a compound heterozygous for IVS 1-5 [G-C] and codon 26 [G-A] beta E mutation in the beta globin gene. Evaluation for iron overload showed severe cardiac iron deposit and severe hepatic iron deposit on MRI T2. MUGA (multigated acquisition scan) scan showed a normal left ventricular function with an ejection-fraction of 56%. Liver and spleen were palpable 4 cm below right and left costal margin respectively.

Elective open splenectomy of patient 3 showed enlarged spleen with multiple splenunculi along the splenic vessels. The drugs prescribed for each patient during hospital stay and their discharge medication is given in Table 2.

Table 2: Drugs prescribed during hospital stay and discharge medication

S.No	Trade Name	Generic Name	Dose	Frequency	Route	Days of treatment
PATIENT 1:						
1.	Inj. Thymoglobulin	Antithymocyte Ig	4.5 mg/kg	1-0-0	IV	D1-D3
2.	Inj. Methotrexate	Methotrexate	100 mg	1-0-1	IV	D1, D3, D6, D11
3.	Inj. Emeset	Ondansetron	4 mg	PRN	IV	D1
4.	T. Pantop	Pantoprazole	20 mg	1-0-0	PO	D1-D3
5.	Inj. Fludarabine	Fludarabine	40 mg/m2	1-0-0	IV	D2-D5
6.	Inj. Magnex	Cefoperazone+ Sulbactum	1 gm	1-0-1	IV	D2
7.	Inj. Amikacin	Amikacin	500 mg	1-0-1	IV	D2
8.	Inj. Cyclosporine	Cyclosporine	2.5 mg/kg	1-0-1	IV	D3-D13
9.	Inj. Thiotepa	Thiotepa	8 mg/kg	1-0-0	IV	D6
10.	Inj. Fluconazole	Fluconazole	2 mg	1-0-0	IV	D10-D18
11.	T. Cyclosporine	Cyclosporine	75 mg	1-0-1	PO	D14
PATIENT 1 DISCHARGE MEDICATIONS:						
1	Syp. Cyclosporine	Cyclosporine	75 mg	1-0-1	Oral	1 week
2	T. Folic acid	Folic acid	2.5 mg	0-0-1	PO	1 week
3	T. Pentids	Penicillin G	2 lakh units	1-0-1	PO	1 week
4	T. Acyclovir	Acyclovir	200 mg	1-1-1-1	PO	1 week
PATIENT 2:						
1	Inj. Thymoglobulin	Antithymocyte Ig	4.5 mg/kg	1-0-0	IV	D1-D3
2	Inj. Fludarabine	Fludarabine	40 mg/m2	1-0-0	IV	D1-D5
3	Inj. Magnex	Cefoperazone+ Sulbactum	1 gm	1-0-1	IV	D2
4	Inj. Emeset	Ondansetron	4 mg	PRN	IV	D1
5	T. Pantop	Pantoprazole	20 mg	1-0-0	PO	D1-D3
6	Inj. Cyclosporine	Cyclosporine	2.5 mg/kg	1-0-1	IV	D2-D8
7	Inj. Thiotepa	Thiotepa	8 mg/kg	1-0-0	IV	D4
PATIENT 2 DISCHARGE MEDICATIONS:						
1	T. Folic acid	Folic acid	2.5 mg	0-0-1	PO	1 week
2	T. Pentids	Penicillin G	2lakh units	1-0-1	PO	1 week
3	Syp. Cyclosporine	Cyclosporine	75 mg	1-0-1	Oral	1 week
4	T. Augmentin	Amoxicillin+ clavulanic acid	500 mg	1-0-1	PO	1 week
5	T. Pantop	Pantoprazole	20 mg	1-0-0	PO	1 week
PATIENT 3:						
1	Inj. Ampicillin	Ampicillin	750 mg	1-1-1-1	IV	D1-D4
2	Inj. Gentamicin	Gentamicin	60 mg	1-1-1	IV	D1-D4
3	Inj Paracetamol	Paracetamol	300 mg	1-1-1-1	IV	D1-D4
4	Inj. Tramadol	Tramadol	25 mg	1-1-1	IV	D1-D4
5	Inj. Pantop	Pantoprazole	40 mg	1-0-1	IV	D1-D4
6	Inj. Morphine	Morphine	2 mg	sos	IV	D2
PATIENT 3 DISCHARGE MEDICATIONS:						
1	T. Folic acid	Folic acid	2.5 mg	0-0-1	PO	1 week
2	T. Pentids	Penicillin G	4 lakh units	1-0-1	PO	1 week
3	Inj. Pneumovac	Pneumococcal vaccine polyvalent	1 amp	Once	IM	Every 5 years
4	T. Pantop	Pantoprazole	20 mg	1-0-0	PO	5 days
5	C. Amoxicillin	Amoxicillin	500 mg	1-1-1	PO	5 days
6	T. Desirox	Deferasirox	500 mg	1-0-0	PO	After 1 week

After bone marrow transplantation, the patients did not develop Graft Versus Host Disease (GvHD). Patient 1 developed a rash which was initially a blanching erythema and later evolved to a follicular rash involving the anterior abdominal wall, chest, and left lower limb. It was associated with itching but no oozing or scaling. It was treated and managed well. The patients were asked to review after 1 week of time.

CONCLUSION

Haemoglobin E-beta thalassemiapatients are treated with lifelong blood transfusion for every 15 to 30 days along with iron chelation therapy. New approaches are being developed to correct the resulting β-globin chain imbalance, in an endeavor to move beyond the lifelong red blood cell transfusion, iron chelation and splenectomy, which impose high costs on healthcare systems.

Reactivation of fetal globin gene with medicinal compounds injected into patients throughout their lives, gene therapy and allogeneic Hematopoietic Stem Cell Transplantation (HSCT) are the 3 approaches envisaged. HSCT is currently the only treatment shown to provide an effective, definitive cure for β-thalassemia. However, this procedure remains perilous and histocompatible donors are recognized for only a small fraction of patients.

The cost of treatment of an 8-year-old thalassemic child is approximately about Rs.1 lakh annually. The only cure available today is bone marrow transplantation, which is largely unaffordable to the majority of the Indian children/parents. Most of these children have a severe clinical presentation but are managed sub-optimally due to lack of monetary resources in majority of the families. To combat the burden of hemoglobinopathies in India, there is an urgent need for the prenatal diagnosis of thalassemia. The important prerequisite for this disorder is to create awareness on the prevalence of β-thalassemia in different ethnic groups and in different regions of the country. Education and screening plays the most important part for the success of prevention programs for the control of thalassemia.

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