Haemoglobin E-beta Thalassaemia in Singapore

Dear Editor,

Haemoglobin E-beta thalassaemia (Hb E/β-thalassaemia) is a common cause of thalassaemia major in Southeast Asia. In Singapore, the prevalence of beta thalassaemia (β-thalassaemia) trait is 0.9% and haemoglobin E (HbE) trait is 0.55% .[1] This is especially high in the Malay ethnic group. According to the National Thalassaemia Registry, the Malay population accounts for 74% of the registered subjects with Hb E/β-thalassaemia.

The clinical and haematological parameters of patients with Hb E/β-thalassaemia are widely disparate, ranging from asymptomatic to severe, life-threatening anemia requiring regular blood transfusions. Its phenotypic variability makes it difficult to predict the course of the disease, especially in the prenatal setting.

Several factors have been suggested to influence the severity of disease. Genetic factors include the genotype of β-thalassaemia,[2] the presence of concomitant alpha thalassaemia (α-thalassemia) and the presence of polymorphism associated with increased foetal haemoglobin (HbF). Environmental influences such as the presence of anti-malarial antibodies have also been implicated.[3]

The aim of this study is to conduct a retrospective case analysis of Hb E/β-thalassaemia cases in our local population.

Materials and Methods

Study Population

The study population includes patients with Hb E/β-thalassaemia referred to the National Thalassaemia Registry in Singapore between 2000 and 2011 and who have been reviewed by a clinician in KK Women's and Children's Hospital.

Data Collection

Records of all patients were reviewed to obtain the following information: demographic data, transfusion and chelation history and history of medical complications. The general surveillance of iron overload in our hospital includes measurement of ferritin, renal and liver function, calcium and phosphate levels, thyroid function test, fasting glucose measurements and cardiac magnetic resonance imaging (MRI T2*). Mean haemoglobin levels, HbF levels, patient's genotype and the presence of concomitant α-thalassemia were also recorded. Severity score for each patient was calculated using the scoring system by Sripichai et al.[4] Approval was obtained from the institutional review board .

Laboratory Methods

Hb electrophoresis was carried out on the Bio-Rad Variant II using the β-thalassaemia short (BTS) programme. β-thalassaemia mutation was determined by screening through 48 mutations reported in the Asian regions using reverse dot blot. For patients with raised HbA_2 but negative for the above mutation, sequencing of β-globin gene was done.

Results

Demographics

Fifty-eight subjects were identified. Patient records were incomplete for 3 patients and 55 patients were recruited into the study. There were 26 females and 29 males. Median age was 13 years (range, 3 to 54 years) at the time of enrollment. The study population consists of 43 Malay, 11 Chinese and 1 Thai patient.

Transfusion and Chelation History

Twenty patients (40%) presented below 3 years old, 26 (47%) presented between the ages of 3 to 10 years old and 7 (13%) presented after 10 years old. Twenty-seven patients were transfusion dependent thalassaemias, with 24 on chelation therapy.

Medical History

Twenty patients (36%) had a splenectomy. Fourteen (25%) patients had developed gallstones and 7 had a cholecystectomy performed. Other medical complications of disease and iron overload are summarised in Table 1.

In addition, 21 out of the 55 patients had a MRI T2* of the heart and liver performed. None had iron loading in the heart. Twenty (98%) patients had evidence of iron loading in the liver. Out of the 20 patients with iron loading in the liver, 7 did not have regular blood transfusions.

Table 1. Medical Complications in Patients (n = 55)

Complication	No. of patients (%)
Hypothyroidism	4 (7.2%)
Hyperparathyroidism	0
Short stature	22 (40%)
Delayed puberty	6 (11%)
Diabetes mellitus	0
Osteoporosis	3 (5.4%)
Pathological fracture	1 (1.8%)
Leg ulcer	1 (1.8%)

Severity Score

The patients were divided into 3 groups according to their severity score. A total of 21 patients belonged to the mild category, 19 to the moderate category and 15 to the severe category.

Mild Category

The mean haemoglobin (Hb) was 8.3 g/dL (range, 6.9 to 10.7 g/dL; SD 1.0). Only one of the patients required occasional transfusions. The mean foetal haemoglobin (HbF) was 35.6% (range, 6.1% to 56.5%; SD 16.1). Two patients underwent splenectomy. MRI T2* imaging was performed for 3 patients. None had cardiac iron overload, but all three had moderate iron load in the liver.

Moderate Category

The mean Hb was 7.4g/dL (range, 6.5 to 9.8 7.4g/dL; SD 1.1) with HbF 39.1% (range, 9.2% to 60.2%; SD 15.2). Two patients had concomitant α-thalassemia.

Thirteen (68%) patients in this category required regular transfusions. Seven required splenectomy. MRI T2* was performed for 8 patients in this category with 4 showing mild, 3 moderate and 1 severe iron loading of the liver.

Severe Category

There were 15 patients in this category. The mean Hb was 6.3 g/dL (range, 5.2 to 7.5 g/dL; SD 0.7). The mean HbF was 44.7% (range, 32% to 64.6%; SD 11.8). One patient had concomitant α-thalassemia. Two patients had passed away at age 13 and 27. Fourteen (93%) patients werere transfusion dependent.

This group of patients had the most complications, accounting for 5 of the 6 patients with delayed puberty and all of the patients with hypothyroidism. Eleven patients had a splenectomy at an average age of 7.6 years. MRI T2* imaging was performed for 10 of these patients with 3 showing mild iron loading of the liver, 4 moderate and 2 severe.

Genotyping of Hb E/β-thalassaemia was performed in 47 patients and is presented in Table 2.

Table 2. β-Thalassaemia Mutations of Patients (n = 47)

	No. of patients in mild category	No. of patients in moderate category	No. of patients in severe category
IVS-1 nt 5 (G/C)	5	7	5
IVS-1 nt 1 (G/T)	1	0	1
Codon 35 (-C)	1	1	2
CDs 41/42 (-TTCT)	1	1	3
Codon 19 (A/G)	2	0	0
-28 TATA box (A/G)	2	0	0
Others	4	6	5
Total no. of patients with genotyping performed	16	15	16

β: Beta

Discussion

Thalassaemia is the most common autosomal recessive condition in Singapore. The phenotypic heterogeneity of Hb E/β-thalassaemia remains a challenge. In our study cohort, 49% of patients with Hb E/β-thalassaemia required regular blood transfusions and most of these patients were on chelation therapy. In previous studies, the percentage of patients requiring regular transfusion ranged from 30% to 57%.[5] Also in our study, 36% of patients required splenectomy. In other case series, the rate of splenectomy ranged from 17% to 50%.

Our patients also had significant medical complications, the most common of which is iron loading of the liver. It is important to note that 35% of these patients did not have regular blood transfusions. This highlights the need to monitor the patients for iron overload regardless of their transfusion status.

When we divided the patients into three different disease severities, there was no clear factor that significantly distinguished the 3 groups. Patients with β^0 mutations, such as CDs 41/42 (-TTCT), CD 35 (-C), CD 17 (A > T), 45 kb Filipino deletion, tend to have higher risk of severe phenotype compared with those with β^+ mutations such as those in IVS-1 and TATA box region, although this correlation is not absolute. As expected, complications of iron overload were most evident in the severe category.

Our study is limited by our small sample population. Another limitation of our study is the potential bias as milder patients may be asymptomatic and therefore not be evaluated in our hospital.

Conclusion

The phenotypic variability of Hb E/β-thalassaemia presents a challenge in counselling and management. In our population, a significant proportion of patients with Hb E/β-thalassaemia have severe disease requiring regular blood transfusions and chelation therapy. There is also a need to closely monitor all patients regardless of their transfusion status.

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