Does Profile of Hemoglobin E β -thalassemia Patients Change After Splenectomy? Experience of a Tertiary Thalassemia Care Centre in Eastern India

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Abstract Hemoglobin E β -thalassemia is by far the commonest form of thalassemia intermedia. Its phenotype ranges from mild anemia to severe transfusion-dependency necessitating splenectomy in many patients. The present study aimed to systematically analyze both clinical as well as laboratory parameters in profile of E β -thalassemia patients after splenectomy in terms of transfusion requirement, infections and other complications. Retrospective study conducted over a period of 3 years included 72 cases of splenectomized E β -thalassaemia patients, considering decrease in transfusion requirements, new complications, antibiotic, anti-malarial prophylaxis and iron chelation therapy. Out of 1380 registered E β -thalassemia patients, 618 (44.78 %) were regularly transfused and 72 (5.22 %) underwent splenectomy. Mean age of diagnosis was 10.3 years. Nineteen patients (26.4 %) underwent splenectomy between 5 and 10 years, 38 cases (52.7 %) between 10 and 20 years. The leading cause (51.39 %) for splenectomy was mechanical discomfort. Mean steady state hemoglobin raised from pre-splenectomy level of 5.43–6.8 gm/dl after splenectomy. Mean transfusion requirement reduced from 18.1 to 7.8 units/year. Mean serum ferritin level increased from 907.58 to 1,091.6 ng/ml. Post-splenectomy; 21 (29.17 %) patients developed facial deformities, 17 (23.6 %) delayed pubertal growth, 11 (15.28 %) venous thromboembolism, five (6.94 %) pulmonary hypertension and four (5.5 %) had extramedullary hematopoiesis. Five (6.96 %) patients had documented bacterial infections and two (2.78 %) suffered

from malaria. Forty eight patients (66.67 %) started with iron chelation therapy; but majority (52.7 %) stopped. Major advantage of splenectomy is reduced transfusion requirement, though it cannot prevent skeletal abnormalities and delayed pubertal growth. In resource constraint countries like India, routine anti-malarial and antibacterial prophylaxis is not desirable; iron chelation therapy should be encouraged and ensured.

Keywords Hb E β -thalassemia · Post-splenectomy complications · Iron chelation therapy

Introduction

Since the classic description of hemoglobin E (HbE) by Chernoff et al. [1], E β -thalassemia has been noted to affect at least a million people worldwide. It is considered to be an important health problem in the Indian subcontinent and Southeast Asia [2, 3]. HbE (β -26 glutamine $\rightarrow$ lysine) is commonest hemoglobin variant in India with prevalence of 7–50 % in Northeastern region and 1–2 % in West Bengal [4]. Various factors decide the outcome of the interplay between the combination of qualitative and quantitative defect of hemoglobin. The clinical picture produced by the interaction is heterogeneous [5]. The marked expansion of erythropoiesis is responsible for much of the pathology of the disease, including hepatosplenomegaly, extramedullary hematopoiesis, bony deformities, growth retardation and delayed sexual maturation [6–8]. Splenomegaly often develops in severely affected patients. In the past, splenectomy was routinely performed in an attempt to increase hemoglobin levels [7]. The present study conducted to assess how post-splenectomy Hb E- β thalassaemia patients progress both in terms of clinical profile as well as

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laboratory investigations. Here we report profile of 72 E β -thalassemia patients who underwent splenectomy.

Materials and Methods

This retrospective study included patients attending thalassemia clinic and thalassemia day care centre for a period of 3 years from July, 2010 to June, 2013. A total of 72 splenectomised E β -thalassemia patients were included in the study. Detailed history including age at diagnosis, first transfusion, splenectomy and transfusion requirements (before and after splenectomy) was taken. As several factors other than splenectomy (e.g. pregnancy, infections, alloimmunization etc.) influences transfusion requirement, they were carefully considered as exclusion criteria in the study. All the patients underwent detailed clinical assessment at least four times in a year (i.e. at 3 months intervals and earlier whenever needed for evaluation of fever or any other complications) including measurement of height, weight, growth velocity, sexual maturation, skeletal deformity. Tanner staging performed every 6 months in the pre-pubescent child and annual bone age films were taken to assess skeletal maturation. Relevant Laboratory parameters assessed included complete blood count (CBC), serum biochemistry and serum ferritin levels done at regular intervals during follow up. Post-splenectomy; steady state hemoglobin (Hb %), serum ferritin levels were compared with that of pre-splenectomy levels. Evidence of other complications was carefully studied by the resources available in our Institute—pulmonary hypertension (PHTN) by echocardiography; thrombo-embolic manifestations (VTE) by compression ultrasonography, extramedullary hematopoiesis (EMH) by MRI in suspected cases (clinical evaluation) after plain film(s) were carefully studied.

Results

The present retrospective study quite methodically analyzed the data over a period of 3 years. It includes a total of 1380 registered E β -thalassemia patients of which 72 were splenectomised. And, in some cases, splenectomy was done outside before enrolment in the study. Out of 1380 E β -thalassemia patients, 618 (44.78 %) were regularly transfused and 72 (5.22 %) underwent splenectomy. Mean age of diagnosis of 72 splenectomised E β -thalassemia patients was 10.3 years (range 3 months–39 years). Ten cases (13.9 %) were diagnosed below 1 year of age, 24 cases (33.3 %) between 1 and 5 years, 23 cases (31.87 %) between 5 and 15 years and 15 cases (20.83 %) above 15 years. The earliest age at first transfusion was one and

half months and the diagnosis were made at 3 months of age (being the earliest diagnosed case). Diagnosis of E β -thalassemia was made as late as 39 years in a male patient requiring blood transfusion for the first time in life (Fig. 1). Thirty five patients (48.57 %) started transfusion below the age of 5 years, 14 cases (19.4 %) between 5 and 10 years, seven cases (9.72 %) between 10 and 15 years and 15 patients (20.83 %) received first transfusion above the age of 15 years. One patient received first transfusion at the age of 39 years (Fig. 1).

Nineteen patients (26.4 %) underwent splenectomy between 5 and 10 years, 38 cases (52.7 %) between 10 and 20 years and 15 patients (20.8 %) above the age of 20 years. In one case, splenectomy was performed at the age of 40 years due to mechanical discomfort caused by huge splenomegaly and increased transfusion requirement. Mechanical discomfort was the leading cause for splenectomy in 37 patients (51.39 %) followed by increased transfusion requirement in 15 cases (20.83 %). In 15 (20.83 %) cases splenectomy was indicated due to mechanical discomfort as well as increased transfusion requirement. In three cases (4.17 %) there was huge splenomegaly and it was operated concurrently during gall bladder stone operation. One patient (1.39 %) had features of hypersplenism with leucopenia and thrombocytopenia and had recurrent attacks of infection and minor bleeding manifestations necessitating splenectomy. In another case (1.39 %), splenectomy was done outside before attending our clinic and the exact cause for operation was not revealed in spite of rigorous searching (Fig. 2).

Pre-splenectomy; steady state mean Hb % level was 5.43 gm/dl (range 3.2–7.6 gm/dl) at the time of first transfusion and/or diagnosis and the majority (66.67 %) had a hemoglobin level below 5.9 gm/dl (Table 1). The steady state mean Hb % level was raised to 6.8 gm/dl (range 5.5–12.3 gm/dl) after splenectomy (Table 1) that took a mean of 4 months (range 2–7 months) after the surgery. Fair number of patients (52.7 %) maintained Hb % level above 7.0 gm/dl after splenectomy (Fig. 3). The observed data comparing steady state mean Hb % level before and after splenectomy, shown Chi square test of difference, χ^2 value = 68.26, p value < 0.00001 (highly significant).

Median number of transfusion requirement was remarkably reduced from 19 units/year pre-splenectomy to 6 units/year after splenectomy. Before splenectomy, majority (74.9 %) of the patients received 11–40 units of blood per year with a maximum of 59 units/year. Post splenectomy; 63.9 % patients received only 1–10 units/year (Fig. 4). Four patients (5.55 %) received single transfusion till date. In one patient, transfusion requirement increased from 12 units/year to 55 units/year after splenectomy. Comparing transfusion requirements before and after splenectomy, the observed data shown Chi square test

Fig. 1 Distribution of age (years) at diagnosis and at first transfusion

Fig. 2 Predominant indication (expressed in *percentage*) for splenectomy

of difference, χ^2 value = 39.7, p value < 0.00001 (highly significant). Mean serum ferritin level increased from 907.58 ng/ml (range: 126–1,682) before splenectomy to 1,091.6 ng/ml (range: 204–2,781) in spite of remarkably reduced transfusion requirement after splenectomy. When compared mean serum ferritin level of before and after

splenectomy, the observed data shown Chi square test of difference, χ^2 value = 7.94, p value = 0.02 (significant).

Post-splenectomy, 21 (29.17 %) patients developed facial deformities and 17 (23.6 %) had delayed pubertal growth. Four (5.5 %) had evidence of EMH, 11 (15.28 %) had VTE and five (6.94 %) developed (PTHN). In the

Table 1 Distribution of cases according to the steady state hemoglobin level before and after splenectomy

Steady state hemoglobin level (gm/dl)	Before splenectomy, n (%)	After splenectomy, n (%)
<3.0	0 (0)	0 (0)
3.0–3.9	6 (8.3)	0 (0)
4–4.9	16 (22.2)	0 (0)
5–5.9	26 (36.1)	2 (2.7)
6–6.9	17 (23.6)	32 (44.4)
7–7.9	7 (9.7)	32 (44.4)
8–10	0 (0)	5 (6.94)
>10	0 (0)	1 (1.36)
–	Total = 72	Total = 72

Fig. 3 Distribution of patients comparing steady state hemoglobin (gm/dl) level before and after splenectomy

present study, only five patients (6.96 %) had documented bacterial infections and two (2.78 %) had suffered from malaria; confirmed by detection of *Plasmodium* spp. on peripheral blood smear examination. Five (6.96 %) patients had documented bacterial infections mostly by gram negative bacteria; severe infections included septicemia, pneumonia, biliary tract infection and urinary tract infection. Organisms isolated were *Escherichia coli* (40 %), *Klebsiella pneumoniae* (20 %), *Pseudomonas* spp. (20 %)

and *Streptococcus pneumoniae* (20 %). Two (2.78 %) had suffered from malaria confirmed by detection of *plasmodium* spp. on the direct smear examination.

Forty eight (66.67 %) patients started with iron chelation therapy and followed up regularly by serial measurement of serum ferritin level; majority (52.7 %) stopped on their own mostly due to financial constraints and only ten patients (13.89 %) were continuing iron chelation therapy regularly.

Fig. 4 Comparison of transfusion requirement (units/year) before and after splenectomy

Discussion

Hb E is caused by a substitution of glutamic acid by lysine at codon 26 of the β -globin gene. This mutation also activates a cryptic mRNA splice site, which results in reduced synthesis of the β -E chain and leads to a thalassemia phenotype. Clinical severity of E-beta thalassemia is variable ranging from mild to severe simulating homozygous β -thalassemia [6, 9, 10].

In our study, 44.78 % patients were regularly transfused and 5.22 % underwent splenectomy. In an analysis of 50 British patients (originating in Bangladesh, India, Pakistan and South East Asia) with E- β -thalassemia, Rees et al. [11] gives an idea of severity of this condition; 50 % of the patients were regularly transfused and nearly 50 % had required splenectomy. Thus, a lesser number of patients in the present study requiring regular transfusion and splenectomy probably are explained by the phenotypic variations in a comparatively homogenous population. Whereas, in another study by Fouladi et al. [12] on 22 Canadian patients, 30 % were regularly transfused and 17 % required splenectomy which in contrast to the present study, included lesser number of patients and probably reflects the other issues in management of thalassemia patients such as trigger for transfusion, recurrent infections etc. Overall, the present study, in comparison to the other studies included more number of cases probably reflects a more real picture in this respect.

The time of onset of symptoms was useful in predicting the long-term clinical phenotype. Severe anemia with symptoms that begin between 6 and 12 months indicated a thalassemia-major phenotype. In the present study, 47.2 % cases were diagnosed below the age of 5 years and 20.83 % above 15 years. The earliest age at first transfusion was one and half months that was diagnosed at the age of 3 months. One patient started blood transfusion at the age of 39 years and subsequently splenectomized after 1 year due to massive splenomegaly and increased blood transfusion. In one study from Uttar Pradesh, India showed the age range in the transfusion dependent group was 2–18 years with 7 out of 11 patients aged below 5 years [13].

The most widely practiced indications for splenectomy in thalassemia are—mechanical discomfort due to huge splenomegaly, increased transfusion demand, poor growth/development and hypersplenism [14]. In our study, the leading cause (51.39 %) for splenectomy was mechanical discomfort due to huge splenomegaly followed by increased transfusion requirement in 20.83 % patients. Pre-splenectomy, mean steady state Hb % level was 5.43 gm/dl (range: 3.2–7.6 gm/dl) at the time of first transfusion and/or diagnosis and the majority (66.67 %) had a hemoglobin level below 5.9 gm/dl. In a brief report by Panigrahi et al. [15] showed the hemoglobin of 23 cases at diagnosis varied from 4.3 to 9.4 g/dL. There was very significant (p value < 0.00001) rise of steady state mean Hb % level after splenectomy.

There has been a considerable decline in the transfusion needs after splenectomy as evidenced by remarkably lesser number of median transfusion requirement. This decrease in transfusion requirement after splenectomy had shown a very high statistical significance (p value). In one patient, requiring increased transfusions after splenectomy, though there was no evidence of extramedullary hemolysis (including spleniculi) at other sites. By achieving Hb % level above 7.0 gm/dl, majority of our patients became transfusion independent or required very infrequent transfusion on demand. Studies earlier had shown that if a diagnosed child is growing poorly and develops facial or other bone abnormalities, and/or when Hb levels are <7 g/dl; regular transfusions will be beneficial [16].

In the present study, mean serum ferritin level increased from 907.58 ng/ml (pre-splenectomy) to 1,091.6 ng/ml (post-splenectomy) in spite of remarkably reduced mean transfusion requirement. The serum ferritin level that was measured serially increased steadily over time even after splenectomy and this increase was statistically significant (p value = 0.02). As established by Gardenghi et al. [17] in beta thalassemia patients, increased GI tract iron absorption can result from severe anemia and ineffective erythropoiesis, which down-regulate the synthesis of hepcidin, a protein that controls iron absorption from the GI tract and increases release of recycled iron from macrophages. Similar mechanism are most likely incriminated in the reportedly increased/higher results of ferritin may play a role in steadily increasing the serum ferritin level in E β -thalassemia patients with decreased transfusion requirements after splenectomy. In the present study, facial deformities and delayed pubertal growth was present in 29.17 and 23.6 % patients respectively. None of the patients on regular follow up reported any episode of bone fracture. Four (5.5 %) patients had evidence of EMH including one with an intradural mass in the D₁₂ region presenting with features of spinal cord compression and another patient had a mass in the urinary bladder presenting with frank hematuria. Ineffective red cell production by the bone marrow (ineffective erythropoiesis) forces expansion of the hematopoietic tissue outside the marrow medulla and leads to hematopoietic compensatory involvement, mostly in the form of masses, of other regions in the body—the phenomenon termed extramedullary hematopoiesis [18]. Olivieri et al. [19] in a review of 109 patients with E β -thalassemia, reported only one patient had a fracture occurred without significant trauma and severe facial deformity was observed in only two patients. Eleven (15.28 %) patients had developed VTE. Tripatara et al. [20] demonstrated the existence of a low grade consumptive coagulopathy among transfused splenectomized patients with severe clinical manifestations, indicating that these patients may have a higher risk for thrombosis than

comparable patients with intact spleen. Prothrombotic hemostatic anomalies, including low levels of coagulation inhibitors, such as protein C and protein S as well as thrombocytosis and platelet activation, have also been observed in these patients [21]. Cardiac ejection fractions and pulmonary artery pressures were measured by 2D transthoracic echocardiography and Doppler study. Five (6.94 %) patients in the study group developed PTHN after splenectomy. Fucharoen et al. [7] reported cardiovascular complications, including congestive heart failure in 11.9 % of cases.

None of our patients were on routine antibacterial and antimalarial prophylaxis. Five (6.96 %) patients had documented bacterial infections and only two (2.78 %) had suffered from malaria. This probably negated the need for a routine antibacterial and anti-malarial prophylaxis. Olivieri et al. [19] in a review of 109 patients with E β -thalassemia, reported only one splenectomized patient with severe life-threatening infections. The predisposing factors of infections in thalassemia include splenectomy, iron overload, anemia, and granulocyte dysfunctions [22].

In the present study, 66.67 % of the patients started with iron chelation therapy having serum ferritin level >500 ng/ml; majority (52.7 %) stopped abruptly mostly due to financial constraints and only 13.89 % were continuing iron chelation therapy regularly. Scope for measuring iron overload by either T2 MRI or liver iron concentration (LIC) is mostly not available in this part of the country. Therefore, physicians have to depend primarily on serum ferritin level in taking decisions regarding iron chelation therapy. Studies by Olivieri et al. [23] of iron loading in affected patients with Hb E β -thalassemia in Sri Lanka, suggest that this disorder is associated with variable, but accelerated, gastrointestinal iron absorption. It was also observed that the iron loading associated with chronic transfusions in patients with Hb E β -thalassemia is similar to that in patients with beta-thalassemia major. Hence, in splenectomized patients, lesser requirement of transfusion at least for some time lessened additional burden of iron overload. But due to other reasons such as accelerated GI iron absorption, regular iron chelation therapy is needed for majority of these patients and to be monitored to minimize the complications related to iron overload. This is a real challenge to the clinicians dedicated in the management of thalassemia patients even after splenectomy.

Conclusion

Haemoglobin E β -thalassaemia is the commonest form of thalassemia intermedia in many Asian countries including India. Though requirement for blood transfusion reduced remarkably after splenectomy in most of the patients,

complications such as facial deformities and delayed pubertal growth could not be prevented. Chances of VTE and PTHN increased. Incidence of bacterial infection and malaria not increased significantly, thus highlighting not to use routine antibacterial and antimalarial prophylaxis. Iron overload is a constant problem even with decreased frequency of blood transfusion after splenectomy. Patients should be encouraged and supported to strictly adhere to regular iron chelation therapy.

Conflict of interest The authors of this paper have no conflicts of interest.

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