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Grade of liver siderosis in beta-thalassaemia major patients receiving different amount of blood transfusion

Souvik Basak, Kashinath Das

Department of General Surgery, Medical College, Kolkata, West Bengal, India

Abstract

Background and objectives: A progressive accumulation of body iron easily occurs as a result of long-term transfusions in patients with anaemia of genetic disorders such as thalassaemia. Iron deposit in liver biopsy sections was studied in beta-thalassaemia major patients to assess the grade of liver siderosis and to correlate the grade with amount of blood transfused.

Materials and methods: Beta-thalassaemia major patients having splenomegaly and selected for splenectomy were enrolled. Liver biopsy was taken from every patient during the splenectomy. Liver tissue was sectioned and stained with Perls' prussian blue method for the presence of iron deposition. The degree of iron deposition was expressed as grades of siderosis from 0 to 4.

Results: A total of 30 beta-thalassemia patients were enrolled in the study. Out of 30 patients, 7 were males (23.3%) and 23 females (76.7%). The mean age of patients was 15.2 ± 1.4 years. The mean serum iron and ferritin levels of the study cases were above the normal range. Blood received by all patients was 51.5 ± 11.6 units (range 31 to 88 units). Out of 30 patients, grade 1, 2, 3 and 4 liver siderosis was present in 1, 3, 9 and 17 patients respectively. Serum ferritin level of patients with grade 4 siderosis was significantly higher ($p = 0.03$) compared to grade 3 cases. Pearson's correlation coefficient test revealed significant positive correlation between grades of liver siderosis and amount of blood transfusion received (0.626, $p < 0.01$).

Conclusion: Grade of liver siderosis is associated with increased units of blood transfusion and is a good indicator for transfusional iron overload in beta-thalassaemia major patients.

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Introduction

The total amount of body iron is approximately 3–4 g, two-thirds of which is composed of red blood cell (RBC) iron and recycled iron by RBC destruction. The remainder is stored as ferritin/hemosiderin, while only 1–2 mg of iron is absorbed in the intestinal tract and circulated in the blood. In the circulation, iron is usually bound to transferrin, and most of the transferrin bound iron is utilized for bone marrow erythropoiesis [1,2]. As there is no active mechanism to excrete iron from the body, a progressive accumulation of body iron easily occurs as a result of long-term transfusions in patients with anaemia of genetic disorders such as thalassaemia.

Hepatic iron overload resulting from multiple red cell transfusions over a long period of time is a complication of thalassaemia major and other congenital anaemia. Liver parenchymal iron overload is usually the result of excessive iron absorption by the enteral route, such as in hereditary hemochromatosis (HHC) and anaemia with ineffective erythropoiesis (iron loading anaemia), but may also reflect enhanced internal redistribution of transfused erythrocyte iron recycled from the reticuloendothelial (RE) cells, as observed in the more advanced stage of transfusional iron overload [3-6]. Organ damage is related to the amount of iron present in the

***Correspondence**: *Dr. Souvik Basak, Department of General Surgery, Medical College, Kolkata, West Bengal, India. Email: sb009cmc@gmail.com*

parenchymal cells, whereas iron within RE cells appears to be relatively innocuous [3,6]. The purpose of this study was to assess grades of liver siderosis in beta-thalassaemia major patients and to correlate the grades with number of units of blood transfused.

Material and methods

Study place and population: The study was an institution-based study conducted in the Department of Surgery, Medical College, Kolkata, India from January 2013 to June 2014 after obtaining approval from Institutional Ethical Committee and informed consent from the patients.

The study enrolled already diagnosed patients of beta-thalassaemia major who were having splenomegaly and being planned for splenectomy. The inclusion criteria were beta-thalassaemia major patients a) requiring repeated blood transfusions (at least 2 per month), b) did not undergone chelation therapy, and c) were more than 12 years of age. Patients having any congenital or acquired liver disease, chronic hepatitis B or hepatitis C infection, malignancy, disease causing splenomegaly, and who refused to be part of the study were excluded. Each enrolled case was clinically examined and detail clinical history was taken using a structured questionnaire. Detail transfusion history and the amount of transfusion received by each patient were recorded.

Determination of liver siderosis: Liver biopsy was taken during splenectomy. Liver biopsy sections were stained with Perls' prussian blue method for iron deposition. The degree of iron deposition/ siderosis was expressed as grades. Grade 0 being negative and grades 1, 2, 3 and 4 represent increasing amounts of stainable iron [7]. Deposits were heaviest in the periphery of the lobule with a concentration gradient toward the centre of the lobule.

Data analysis: Data were analysed with SPSS® software version 26 for Windows 11 (SPSS, Chicago, IL, USA). Apart from descriptive statistics nonparametric Kruskal-Wallis test was performed to compare among the different groups. Pearson's correlation coefficient was performed to test the relationship between the grade of siderosis and amount of blood transfused.

Results

In this study, 30 beta-thalassaemia major patients were included. Out of 30 patients, 7 were males (23%) and 23 females (77%). The mean age of patients was 15.2 ± 1.4 years (Table-1). Detail results of MCV, MCH, MCHC, serum iron and ferritin of the study population are shown in Table-1. The mean serum iron and ferritin levels of the study cases were above the normal range.

Table-1: *Baseline blood parameters of study population (n = 30)*

Variables	Mean ± SD (Range)
Age (Years)	15.2 ± 1.4 (12-18)
MCV (fL)	76.3 ± 4.3 (68.5-84.4)
MCH (pg)	23.3 ± 1.9 (19.6-28.1)
MCHC (g/dL)	30.5 ± 1.2 (28.6-34.1)
Serum iron (µg/dL)	206.7 ± 27.9 (89-254)
Serum ferritin (ng/mL)	1755.9 ± 595.5 (1008-4075)
TIBC (µg/dL)	257.6 ± 27.3 (206-312)

Note: MCV – mean corpuscular volume, MCH – mean corpuscular haemoglobin, MCHC – mean corpuscular haemoglobin concentration, TIBC – total iron binding capacity.

Out of 30 patients, one patient had grade 1 liver siderosis and grade 2, 3 and 4 liver siderosis was present in 3, 9 and 17 patients respectively (Table-2). The mean age of patients having grade 1, 2, 3 and 4 liver siderosis were 16, 15.3 ± 2.3, 14.8 ± 1.2 and 15.4 ± 1.5 years respectively. There was no significant difference of age of the patients belonging to four grades. There were no significant differences in MCV, MCH, MCHC, serum iron and

Table-2: *Comparison of blood parameters and iron studies of patients with different grades of liver siderosis*

Grade of siderosis	No. of cases (%)	Mean ± SD value of					
		MCV (fL)	MCH (pg)	MCHC (g/dL)	S. iron (µg/dL)	S. ferritin* (ng/mL)	TIBC (µg/dL)
1	1 (3.3)	73.0	22.2 ±	30.4	188.0	1008.0	248.0
2	3 (10)	73.6 ± 2.3	21.9 ± 0.9	29.8 ± 0.3	212.3 ± 15.9	1298.0 ± 83.8	282.7 ± 13.3
3	9 (30)	75.7 ± 4.6	22.9 ± 1.9	30.3 ± 1.2	193.9 ± 40.4	1435.1 ± 188.2	261.5 ± 35.5
4	17 (56.7)	77.3 ± 4.4	23.8 ± 1.9	30.8 ± 1.2	213.7 ± 19.8	2050.6 ± 632.2	251.7 ± 23.1

*Note: *compared among the groups by ANOVA; Grade 3 vs. 4: p = 0.03.*

TIBC among patients having different grades of liver siderosis. Serum ferritin was more than the normal range in patients with grade 1 to 4 siderosis. Serum ferritin level of patients having grade 4 siderosis was significantly higher (p = 0.03) compared to grade 3 cases. However, serum ferritin levels of patients having grade 1, 2 and 3 were not significantly different from each other (p > 0.05).

Table-3 shows the unit of blood transfusion received by patients with different grades of liver siderosis. Total 51.5 ± 11.6 units of blood were

Table-3: *Unit of blood transfusion received by patients having different grades of liver siderosis*

Grade of siderosis	Number of cases	Units of blood transfused	p value*
		Mean ± SD	
1	1	31.0	
2	3	40.7 ± 3.1	
3	9	46.6 ± 5.5	0.003
4	17	57.3 ± 11.4	
Total	30	51.5 ± 11.6	

*Note: *Kruskal-Wallis test*

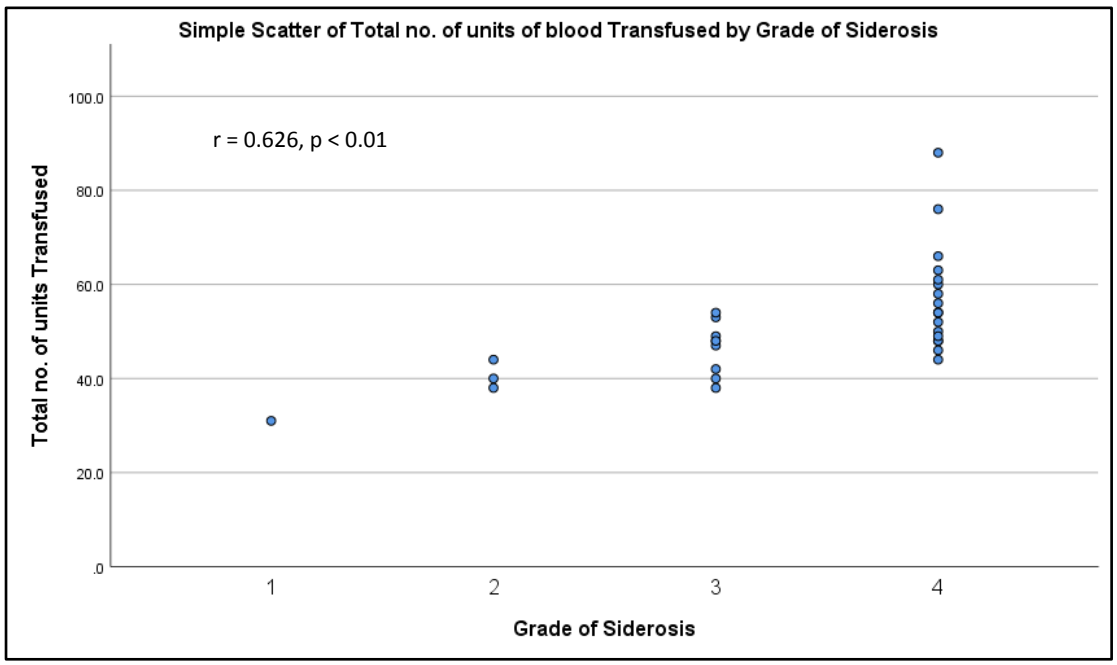

Figure-1: *Pearson correlation between amount of transfusion units and grades of siderosis*

received by all patients (range 31 to 88 units). Recipient of more units of blood transfusion had higher grade of liver siderosis. Patients having grade 4 siderosis received significantly more units of blood transfusion compared to patients of other grades. Pearson's correlation coefficient test revealed that there was significant positive correlation between grades of liver siderosis and amount of transfusion received ($r = 0.626$, $p < 0.01$; Figure-1).

Discussion

In our study, 30 beta-thalassaemia major patients, fulfilling the selection criteria, were studied for the presence of liver siderosis and were correlated with the amount of blood transfusion received by them. In our study, the values of MCV, MCH and MCHC were below their normal values which were expected findings in these patients as these RBC indices decrease in microcytic hypochromic anaemia like thalassaemia. There were no significant differences in MCV, MCH, MCHC, serum iron and TIBC values among patients having differing grades of liver siderosis. However, serum ferritin was high in all the cases with different grades of liver siderosis. This finding is consistent with the findings of Takatoku *et al* [8]. However, the level of serum ferritin is also affected by acute and chronic inflammation and infections. Other clinical conditions such as inflammation and malignancy should be excluded for appropriate interpretation of the values of serum ferritin for the assessment of body iron status when serum ferritin is used as a biological marker for evaluation of body iron stores [9].

In beta-thalassaemia major, abnormalities in haemoglobin decrease erythrocyte life span and the pool of erythrocyte precursors is markedly expanded, leading to increased enteral absorption of dietary iron [4,6,10]. Aggressive transfusion therapy suppresses endogenous erythropoiesis and corrects the severe anaemia, but leads to its own complications, the worst of which is iron overload [11,12]. In the present study, majority cases had grade 4 liver siderosis. It could be due to their late presentation which was evident by high serum ferritin level and repeated monthly blood transfusions (> 2). Repeated transfusion increases iron deposition in liver resulting into increased grade of liver siderosis. Increasing the awareness of both patients and their first points of contact like primary health workers must be done to minimize irreversible organ damage and subsequent complications. Non-invasive methods for the assessment of hemosiderosis should be considered to detect early deposition of iron in liver to prevent lasting organ damage. Blood chelating agents should be started at appropriate time so that the chances of patients ending up for surgery can be minimized. According to Deugnier *et al*, patients of hereditary hemochromatosis have an estimated 240-fold increased relative risk of developing hepatocellular carcinoma, with the degree of risk correlating with the amount and duration of iron overload and degree of fibrosis [13]. Though mechanism of hemosiderosis is different in thalassaemia and hereditary hemochromatosis it cannot be ignored that iron deposition *per se* can have several liver related complications, even life-threatening ones and further research is necessary in this regard.

So, grade of liver siderosis can be a good indicator for transfusional iron overload in beta-thalassaemia major patients. Further research is necessary with regard to iron deposition in non-hepatic organs to properly assess the progress of disease and to determine timing for aggressive therapy.

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