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Liver Function In Pediatric β-Thalassemia Major Patients Receiving Multiple Blood Transfusions

KEYWORDS: thalassemia, ferritin,liver.

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ABSTRACT *Background- Beta –thalassemia major is an autosomal recessive disease that leads to severe hemolytic anemia in early infancy. Repetitive blood transfusion leads to iron overload which adversely affect the function of liver, heart and endocrine glands.*

Objective-The aim of the present study was to investigate the impairment in liver function with the increased iron overload in pediatric patients of β- thalassemia major.

Methods-The analyzed group consisted 50 subjects and 50 controls further divided in two age groups i.e. I and II. Ferritin was measured by ferrozine method.

Results-Thalassemic subjects have significantly higher ferritin, AST,ALT and bilirubin level. Albumin level was found to be significantly reduced showing impaired liver function.

Conclusions- Repetitive blood transfusions leads to iron overload in thalassemic children causing significant damage to liver resulting in elevated level of ferritin, AST, ALT and bilirubin and reduced synthetic capacity of albumin.

Introduction

Thalassemias are a group of inherited autosomal recessive disorders caused by defects in the synthesis of one or more of the hemoglobin chains. Imbalance of globin chains cause hemolysis and impair erythropoiesis(1).

Thalassemia major is the severe transfusion dependent form and major cause of morbidity and mortality in these thalassemic are anemia and iron overload. Studies have shown that the overall prevalence of β-thalassaemia in India is 3-4% with an estimate of around 8,000 to 10,000 new births with major disease each year (2)

The progressive iron overload observed in β-thalassemia major patients is the side effect of ineffective erythropoiesis, increased gastrointestinal absorption of iron , lack of physiological mechanism for excreting excess iron , lack of physiological mechanism for excreting excess iron and multiple blood transfusions which results in hemochromatosis. Even elevated body iron load is observed in milder form of thalassemia (3).

Iron has a catalytic role to produce powerful reactive oxidant species (ROS) and free radicals, which lead to oxidative damage (4).Antioxidants plays an essential role in protection of the cells from oxidative damage (5).

Transfused iron is deposited first within the reticuloendothelial cells prior to parenchymal iron loading within the heart and liver. Effective management of iron overload requires frequent evaluation of the body iron stores (6).

During the last years, liver disease has emerged as a major cause of mortality in patients with β-thalassaemia major(2). Liver disease in these patients can manifest as hepatomegaly, increased aspartate and alanine transaminase activities, hepatitis B and C (7). Significant fibrosis is frequent and its progression is mostly influenced by iron overload which may be attributable to hypertransfusion, inadequate chelation, erythrocyte catabolism and excessive iron absorption from the gut as a consequence of ineffective erythropoiesis(8). Hepatocytes are the major storage site for body iron, so with iron overload, these cells are relentlessly bombarded by reactive oxygen species and eventually die. Damage to these cells (hepatocytes) start to accumulate within a year of commencing transfusion therapy after as few as 10–20 transfusions(9).In present study our aim was to investigate liver function test (Bilirubin, AST, ALT, Total protein and Albumin) and serum ferritin with routine hematological parameters(Hb, MCV,MCH,RDW).

Materials and Methods

This study was conducted in Department of Biochemistry Jhalawar Hospital and medical college, Jhalawar. A total of 50 clinically diagnosed β- thalassemia major children (1-14 years) were randomly selected irrespective of their gender, which were on regular blood transfusion therapy. 50 healthy age matched controls were selected and for the sake of convenience, patients and controls were divided in two age groups i.e. Age group I. 1-3years and Age group II. 4-14 years. Written consent was taken from parents/ guardians. The work was approved by ethical committee of SRG Hospital and Medical College.

Exclusion and Inclusion criteria- Patients with a confirmed diagnosis of β- thalassemia major between 1-14 years were selected, who were on blood transfusion and iron chelation therapy. Exclusion criteria included (1).Thalassemia trait or intermedia (2). History of Jaundice due to viral hepatitis (3). History of splenectomy (4). Positive screening test for hepatitis C or B.

Experimentals - Blood was collected in EDTA vial for hematological estimations and in plain vial for estimation of other parameters in sera.

CBC was done on automated cell counter. Total protein, albumin, bilirubin, AST, ALT and ferritin were estimated by using commercial logotech diagnostic kits on autoanalyzer. Mean and SD were calculated and student's t-test (un-

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paired) was used to compare the two groups. $p<0.05$ was considered statistically significant.

Results

Red cell indices and biochemical parameters of control and thalassemic subjects for age group I are given in table-1 and for age group II in table-II.

Table (1):Comparison of measured parameters between control and thalassemic subjects in age group I(1-3 years)

Parameters	Control (n=22) Mean±SD	Thalassemia (n=22) Mean±SD	p-value
Hb	11.78±0.30	6.43±1.76	<0.0001
MCV	82.23±4.70	76.50 ±8.53	0.0161
MCH	29.01±3.13	23.18 ±2.83	<0.0001
RDW	12.56±0.66	20.60±3.93	<0.0001
Total protein	7.16±1.56	6.50±0.35	0.1606
Albumin	4.47±0.32	3.77±0.54	<0.0001
Bilirubin	0.47±0.23	1.65±0.88	<0.0001
AST	18.64±5.84	83.58±63.95	<0.0001
ALT	18.32±6.90	82.67±70.91	0.0002
Ferritin	47.14 ±8.29	1725.17±521.19	<0.0001

Table (2): Comparison of measured parameters between control and thalassemic subjects in age group II (4-14 years)

Parameters	Control (n=28) Mean±SD	Thalassemia (n=28) Mean±SD	p-value
Hb	12.57±0.47	5.96±1.31	<0.0001
MCV	84.85±5.12	77.00 ±6.07	<0.0001
MCH	29.66 ±2.66	23.11 ±2.07	<0.0001
RDW	12.36±0.65	19.33± 5.27	<0.0001
Total protein	7.72±0.40	6.66±0.35	<0.0001
Albumin	4.56 ±0.31	3.86 ±0.45	<0.0001
Bilirubin	0.48±0.19	2.01±1.02	<0.0001
AST	19.25±6.39	73.15±42.77	<0.0001
ALT	18.86±7.51	59.69±34.60	<0.0001
Ferritin	51.46±7.99	1813.62 ±627.01	<0.0001

Highly significant reduction($p<0.0001$) was observed in hemoglobin level in thalassemic subjects as compared to control in both age groups .Significant decrease in MCV and MCH was observed in age group I(MCV=76.50 ±8.53, MCH=23.18 ±2.83) and II (MCV=77.00 ±6.07, MCH=23.11 ±2.07) as compared to control. Significant reduction in albumin level was observed in thalassemic subjects of both age groups ($p<0.0001$) as compared to control. The level of bilirubin, AST, ALT and ferritin was found to be significantly elevated in thalassemic subjects of both age groups as compared to controls with observed $p<0.0001$.The level of ferritin was found to be elevated several folds in age group I and II with mean ± SD of 1725.17 ± 521.19 and 1813.62 ± 627.01 as comaperd to control 47.14 ± 8.29 and 51.46 ± 7.99, respectively.

Discussion

The clinical utility of biochemical screening using multiple parameters has often been used to assess the functions of many organs in the body. The aim of the present study was to investigate the impairment in liver function with increased iron overload in pediatric patients of β- thalassemia major.

A highly significant elevation in AST and ALT was observed in thalassemic subjects the possible reason behind above findings could be, repetitive transfusions resulted in iron overload, 70% of the iron being stored in liver causing hepatocellular damage, this injury to the liver cells causes leakage of the enzymes in the circulation as a result of hepatic necro-inflammation (10, 11).

A general decrease in Total protein and albumin level was observed in this study. The possible cause of decreased serum total protein and albumin is due to secondarily decreased synthesis of protein by the liver (12,13). In thalassemia due to deposition of iron in hepatocytes the synthesis of albumin gets reduced, due to renal damage albuminuria occurs and due to inadequate nutrition, condition worsens(14).

The observed increase in bilirubin may be related to hemolytic process and existing hepatic damage. The ineffective erythropoiesis and repetitive blood transfusion results in increased bilirubin and due to deposition of iron in liver the capacity to conjugate bilirubin is also affected(15). Being an antioxidant, its level is elevated in serum due to oxidative stress of thalassemia(16). β-thalassemic children could potentially induce hepatic toxicity, and consequently increased bilirubin level, that arises from decrease in activity of cythochrome c oxidase disrupting the mitochondrial respiration (17).

In thalassemic children elevated level of ferritin was found. It may be due to a number of reasons, including repetitive blood transfusions, peripheral hemolysis, increased intestinal iron absorption as well as ineffective erythropoiesis(18,19,20). Ferritin is a positive acute phase protein, level of which may elevate in infection or inflammation. In the absence of inflammation or liver disease, high serum ferritin concentration indicate iron overload (21).

Conclusions

Hepatomegaly is one of the most common findings in thalassemic patient that induced with hemosiderosis, extra medullary hematopoiesis, transmitted hepatitis B and C and cirrhosis.

Disturbance of liver function observed in thalassemic patients do confirm the decrease in protein synthesis by the liver. In addition, elevation of liver protein enzymes in thalassemic patients further supports this view. Higher ferritin level in age group II suggests increased iron load with number of blood transfusions in spite of chelation therapy.

Recommendations

Reevaluation of the current protocol of chelation therapy is needed to protect the liver damage due to repetitive blood transfusions in early childhood.

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