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Research Article

Screening of liver disease in children with transfusion dependent thalassemia at Minia University Hospitals

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Abstract

Background: Beta thalassemia is a hereditary disorder that results from genetic mutations in the synthesis of beta-globin chains. The imbalance of globin chain synthesis results in aggregates that damage red cell membranes, resulting in intravascular hemolysis. This results in chronic anemia which causes erythroid hyperplasia and extramedullary hematopoiesis. "TDT" patients are liable for several medical complications .liver disease is among the most important of them. This study aims to assess the prevalence of liver disease in children with transfusion-dependent thalassemia at Minia University Hospitals. **Methods:** This study included 60 children diagnosed with TDT and on deferasirox and another healthy 60 children as control. We assessed ALT, AST, HCV Abs, serum ferritin. **Results:** Mean ALT (iu/l) was 77.5±54.2, mean AST (iu/l) was 66.3±42.04 and mean serum ferritin (ng/ml) was 4282.5±2612. HCV Abs were positive in 12(20%) of cases. **Conclusion:** TDT patients at Minia University Hospitals have elevated liver enzymes and 20% of them are HCV positive.

Keywords: Screening, liver disease, transfusion-dependent- thalassemia, Children

Introduction

Beta thalassemia is an autosomal recessive disorder that results from genetic deficiency in the synthesis of beta-globin chains. There are more than 200 known mutations in beta globin gene that cause thalassemia thus it has wide spectrum of severity.[1] Clinically, beta thalassemia syndromes are classified into thalassemia trait, transfusion dependent thalassemia "TDT" or non-transfusion-dependent thalassemia "NTDT". [2]

The severe imbalance of globin chain synthesis (alpha >> beta) results in excess unpaired alphaglobin chains aggregate to form precipitates that damage red cell membranes, resulting in intravascular hemolysis, intra-medullary death and ineffective erythropoiesis. This results in chronic microcytic hypochromic anemia which causes erythroid hyperplasia and extramedullary hematopoiesis. [3]

"TDT" patients are liable for several medical complications that can lead to death. Liver disease is among the most important and common of them. Common risk factors for this are extramedullary hematopoiesis, hepatic iron overload.[4], infection with hepatitis virus[5] and chelation therapy toxicity [6].

This study aims to assess the prevalence of liver disease in children with transfusion-dependent thalassemia at Minia University Hospitals.

Patients and Methods

This cross-sectional study was carried out at the Pediatric department, Minia University Children Hospital, Faculty of Medicine, Minia University, from September 2019 till May 2021. It included 60 children diagnosed with transfusion-dependent thalassemia, based on previous hemoglobin electrophoresis and clinical course. They were recruited from the pediatric hematology outpatient clinic and

pediatric hematology in-patient ward. All patients were on a regular blood transfusion program every 2 - 6 weeks and on deferasirox iron chelation therapy for at least 12 months before participating in the study. Age ranged between 5 and 16 years, and there was no sex predilection.

The study also included another 60 children, apparently healthy, age and sex matched with the previous group served as control group.
They were selected from general outpatient pediatric clinics. Children with any chronic disease other than TDT, or refused to participate were excluded from the study.

Data collection:
Baseline clinical assessment
All included children were subjected to detailed medical history taking and thorough clinical examination with particular emphasis on the history of the age of the first transfusion, transfusion burden/year (ml/kg/year), and history of splenectomy, the average frequency of transfusion, and type and duration of chelation therapy.
Children with any chronic disease other than TDT, or refused to participate were excluded from the study.
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Children with any chronic disease other than TDT, or refused to participate were excluded from the study. The following laboratory investigations were done, CBC, serum ferritin, liver function tests, and hepatitis C virus antibodies.

About 6 ml of venous blood were withdrawn from each subject by sterile venipuncture, 2 ml were collected on two sterile vacutainers containing EDTA solutions tubes, this tube was used for CBC assay by an automated cell counter (CelltacES, Nihon Kohden, Germany). The remaining 4 ml were put on serum separator gel tubes then were allowed to clot for 30 minutes at 37ºC before centrifugation for 15 minutes at 3,500 rpm. The expressed serum measured serum ferritin using fully automated clinical chemistry auto-analyzer system Konelab 60i (Thermo Electron Incorporation, Finland).

Liver function tests were tested by Synchron LX20 automated multi-channel analyzer (Beckman Coulter, Fulleton, CA).
HCV-Abs were tested using the Architect i4000 SR (Abbott, Chicago, Illinois).

Ethics approval and consent to participate
The Ethical Committee of the Faculty of Medicine, Minia University, approved this study. Written consents from the patients' caregivers were obtained. All the participants were given the right to withdraw from our research at any point they desired.

Statistical Data Analysis
Data will be coded, entered, and analyzed using SPSS (statistical package for social sciences) version 20. Descriptive statistics were calculated and expressed as mean±standard deviation (SD) for quantitative data and as number and percent for qualitative data. Analytical statistics were done by using Independent sample t-test (comparison of quantitative data between two groups). p-value <0.05 was considered significant.

Results
In this study, 38 (63.3%) of the studied TDT children were males, their mean age was 13 ± 4.1 years, and 32 (53.3%) of them were a result of a consanguineous marriage. TDT children had significantly lower BMI (p=0.04) and significantly more frequent hepatosplenomegaly (p <0.001 for both) than controls. (Table 1) Their mean age of starting blood transfusion was 19.2± 9 months, their mean age of starting chelation therapy was 7±4.2 years and 34 (57%) of them were splenectomized. None of them had manifestations of decompensation. (Table 2)

Regarding the main laboratory investigations, TDT children had significantly lower Hb level,

and significantly higher liver enzymes and serum ferritin than controls (p<0.001 for all). TDT children were also more frequently to test positive for HCV Abs than controls (p<0.001). (Table 3)

Table 1: Demographic and clinical data of TDT children and control

Variables	TDT children N = 60	Control N = 60	p-value
Age (years): Mean ±SD	13 ± 4.1	13.3±4	0.6
Sex: Male: n (%)	38(63.3%)	32(53.3%)	0.3
Consanguinity: Positive: n (%)	32(53.3%)	32(53.3%)	**1.000**
BMI: Mean ±SD	17.4± 2.8	19.3±15.4	**0.04***
Liver: Hepatomegaly: n (%)	38(63.3%)	0(0%)	**<0.001***
Spleen: Splenomegaly: n (%)	18(30%)	0(0%)	**<0.001***

BMI: body mass index
* Statistical significance< 0.05

Table 2: Additional clinical data of the studied TDT children

Variable	N= 60
Age of start blood transfusion (months): Mean ±SD	19.2 ±19
Pre transfusion Hb (gm%): Mean ±SD	6 ±0.7
Splenectomy: Yes: n (%)	34(57%)
Age of start chelation therapy (years): Mean ±SD	7±4.2

Hb: hemoglobin
* Statistical significance< 0.05

Table 3: Laboratory data of TDT children and control

Variables	TDT children N = 60	Control N = 60	p-value
Hb (gm%): Mean ±SD	9.4±0.9	11.1±0.9	**<0.001***
ALT (iu/l): Mean ±SD	77.5±54.2	19.03±4.5	**<0.001***
AST (iu/l): Mean ±SD	66.3±42.04	22.5±5.3	**<0.001***
Ferritin (ng/ml): Mean ±SD	4282.5±2612	34.2 ±13	**<0.001***
HCV Abs: Positive: n (%)	12(20%)	0(0%)	**<0.001***

ALT: alanine-amino transferase; AST: aspartase-transferase;
HCV Abs: hepatitis C virus antibodies.
* Statistical significance< 0.05

Discussion

Liver disease is one of the most important and common complications in TDT patients. Common risk factors for this are extramedullary hematopoiesis, hepatic iron overload[4], infection with hepatitis virus[5] and chelation therapy toxicity[6].

Our study demonstrated that TDT children had elevated ALT, AST and serum ferritin levels. Our results are compatible with results of Moshary et al.,[7] who found increased liver enzymes in their patients and confirmed that iron deposition is the ultimate reason for it.

Also, Abdelrahman et al.,[8] study reported that hepatic affection is common in TDT patients and is more profound in patients with iron overload and those with chronic hepatitis C infection. Previous studies revealed that iron

deposition is associated with increased oxidative stress, lipid peroxidation, and liver cell damage. [9] and the liver play an important role in iron metabolism in the whole body.[10]

HCV Abs were positive in 20% of our cases which is in agreement with El -Shansory et al.,[11] who demonstrated that TDT children more frequently test positive for HCV Abs which is mostly transfusion acquired infection. Kountouras et al.,[12] reported that HCV infection is the major cause of liver damage in patients with TDT.

Contradictory to our results, 20% of our patients were positive for HCV Abs which is lower compared with previous studies; for example, in a study conducted by Salama et al.,[4] 50% of patients were positive for HCV Abs. The lower prevalence in this study may be owing to the relatively young age of studied patients and also the effective screening of blood and blood products.

Moreover, Galeotti et al.,[13] study on deferisorex reported that it is significantly correlated with hepatic toxicities and attributed that to its pharmacokinetics which were significantly influenced by many factors like lean body mass (bioavailability and absorption constant), body weight (volume of distribution) and serum creatinine (clearance). In disagreement with our results, several studies reported that deferasirox therapy decreases iron overload and improves liver enzymes[14], others found that 9 elevated ALT after deferasirox therapy was short lived and lasted for 4 weeks in 95.5% of patients.[15]

Conclusion

We concluded that TDT patients at Minia University Hospitals have elevated liver enzymes and 20% of them are HCV positive.

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