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A CLINICO-HAEMATOLOGICAL STUDY OF TRANSFUSION DEPENDENT B THALASSEMIA CHILDREN ATTENDING A BLOOD TRANSFUSION CENTER IN ELURU, WEST GODAVARI DISTRICT. A.P.

Paediatrics

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ABSTRACT

BACKGROUND: Thalassemia syndromes are a group of hereditary blood disorders characterized by reduced or absent globin chain synthesis, resulting in reduced hemoglobin in red blood cells, decreased RBC production and anemia. In India over 20 million people have thalassemia gene. It has been estimated that over 6000-8000 children, who are homozygotes of β thalassemia are born in India every year and unfortunately most of these children die either undiagnosed because of inadequate facilities, poor management and financial constraints.

OBJECTIVE: To study the Clinico-haematological profile of transfusion dependent β thalassemia children between 2-18 years of age presenting to the transfusion center. Very limited data has been available in this region regarding any correlation between serum ferritin and liver enzymes, renal function tests, Serum vitamin D3 and hence this study was undertaken.

METHODOLOGY: This is a cross sectional observational study in 77 transfusion dependent β thalassemia major children in the age group of 2 to 18 years where mean values of liver enzymes, renal function tests, thyroid profile, serum vitamin D3 levels were analyzed and correlated with average serum ferritin levels.

RESULTS: Elevated S.ferritin has shown a strong correlation with high levels of liver enzymes.B.Urea has shown some significant correlation with S.ferritin.Mean values of average ferritin (ng/ml): 2918±1826, S.Globulin (gm/dl): 2±0.92, S. albumin(gm/dl):4±0.82, A/G ratio: 3±1.9, ALP (IU/L): 144±71.5, AAT(IU/L): 45±25.8, AST (IU/L): 35±16.8, B.Urea (mg/dl): 18±12.4, S.creatinine (mg/dl): 0.8±1.7, S.T3 (pg/ml): 1.5±0.5, S.T4 (ng/ml): 9.8±9.7, S.TSH(mIU/L): 2.1±2.8 and S.Vit D3(ng/ml): 32.4±14.3

CONCLUSION: Thalassemia syndromes are an important cause of morbidity and mortality in children. With increase in number of transfusions, derangement of LFT, KFT and Serum Ferritin has been observed. Hence thalassemic children requiring regular blood transfusion need better strategies for removing excess Iron from their body.

KEYWORDS

Beta thalassemia major, Blood transfusion, Serum ferritin, Liver function tests

INTRODUCTION:

Beta (β) thalassemia syndromes are a group of hereditary blood disorders characterized by reduced or absent β globin chain synthesis, resulting in reduced hemoglobin in red blood cells, decreased RBC production and anemia. Most thalassemia are inherited as recessive traits, βthalassemia is caused by the reduced (β^+) or absent (β^0) synthesis of the β globin chains of the hemoglobin tetramer, which is made up of two α globin and two β globin chains (α_2, β_2). Three clinical and haematological conditions of increasing severity are recognized, i.e. thalassemia carrier state, thalassemia intermedia and thalassemia major[1].

Although reliable data are still lacking for many regions of the world, recent data indicate that about 7% of the world's population is a carrier of a hemoglobin disorder, and that 3,00,000-5,00,000 children are born each year with the severe homozygous state of the disease worldwide. Every year approximately 1,00,000 are born with thalassemia in India. The carrier rate for thalassemia gene varies from 1-3% in southern India to 3-15% in Northern India[1].

Children with β thalassemia usually become symptomatic during 2nd to 6th month of life. Fatigue, poor appetite, and lethargy are late findings of severe anemia in an infant or children before transfusion therapy. The findings in severe thalassemia includes typical facies (maxillary hyperplasia, flat nasal bridge, frontal bossing), pathologic bone fracture, marked hepatosplenomegaly, and cachexia. The spleen may become so enlarged that it causes mechanical discomfort and secondary hypersplenism. These classical findings are primarily seen in developing countries[2].

Many of these features became less severe and less frequent with blood transfusion. Endocrine and cardiac pathology is often associated with excessive iron stores in patients with thalassemia major who are chronically transfused. Common endocrine dysfunctions are hypothyroidism, gonadal failure, and diabetes mellitus. Most infants and children have cardiac decompensation when the hemoglobin is 4.0 g/dL or less. The diagnosis of thalassemia is initially suggested by clinical findings, family history and the results of routine hematological profile and confirmed by Hb Electrophoresis. Structural hemoglobinopathy have an impact on RBC indices e.g. Hb, MCV, RDW, RBC number are critical to diagnosis[2].

In India over 20 million people have thalassemia gene. It has been estimated that over 6000-8000 children, who are homozygotes of β thalassemia are born in India every year and unfortunately most of these children die either undiagnosed because of inadequate facilities, poor management and financial constraints[3].

So, all these children require regular monitoring and we need awareness of the burden of disease to evolve regular detection, management and prevention strategies. With this background, this study was done in transfusion centre, Eluru town.

OBJECTIVE:

To study the Clinico-haematological profile of transfusion dependent β thalassemia children between 2- 18 years of age, presenting to a transfusion center.

To study if there is any correlation between serum ferritin and liver enzymes, renal function tests, vitamin D3.

METHODOLOGY:

INCLUSION CRITERIA:
All diagnosed β thalassemia major patients between age group of 2 to 18 years and attending Red Cross transfusion centre, Eluru and receiving regular transfusion.

EXCLUSION CRITERIA:
- Patients less than 2 years and more than 18 years
- Children having multiple congenital anomalies along with β thalassemia major
- Coexisting cardiac or pulmonary disease
- Chronic haemolytic anaemia other than β thalassemia major
- Thalassemia minor
- β thalassemia with any other haemolytic anaemia

This cross sectional study was carried out in children with clinical presentation suggestive of haemoglobinopathies from April 2019 to September 2019 in Red cross recognized transfusion centre located in District hospital, Eluru. 77 transfusion dependant beta thalassemia children of both sexes between 2 to 18 years of age were the population under study. Three ml of EDTA anti coagulated blood was drawn from all the cases with proper aseptic precautions.

The samples were analysed for multi parameter haemogram including haemoglobin, haematocrit, MCV, MCH, MCHC, RDW, RBC Count, WBC Count, Platelet Count, Reticulocyte Count, Ferritin levels, S.protein, S.albumin, S.globulin, A/G ratio, ALP, AAT, AST, B.urea, S.creatinine, S.T3, S.T4, S.TSH, S.vit. D3.

Peripheral blood smears were stained using Leishman stain in all cases and details of differential count and red cell morphological alterations seen. Hb type and quantification was performed by high performance liquid chromatography

The information regarding socio-demographic details of the patients, type of thalassemia, risk factors such as family history of genetic disorders, history of consanguinity among parents, symptoms, signs, and complications associated with thalassemia, hematological reports, and management practices were recorded in a predesigned validated pro forma. Data were entered and analysed using SPSS Inc., Chicago, IL Version 23.0., Pearson correlation, Paired T test were used to test association between variables. Ap value of <0.05 was considered statistically significant association.

RESULTS:
Sex distribution:
Table and violin graph showing sex distribution in thalassemia children.

Table: 1

Gender	Number	Percentage
Male	48	62.3%
Female	29	37.7%

Fig: 1

Table .2: Age distribution

Age at Diagnosis	Number	Percentage
0-6 months	51	66.2%
6-12 months	18	23.4%
>12 months	8	10.4%

Table 3: Levels of LFT, RFT, Thyroid profile, Vit.D3 in thalassemia major children

	Mean	SD
Ferritin_Avg	2918.325	1826.101
S_Protein_Tot	6.689	0.573
S_Alb	4.235	0.821
S_Glob	2.454	0.922
A_G_ratio	3.331	1.955
ALP	144.570	71.514
AAT	45.839	25.873
AST	35.148	16.811
Bl_Urea	18.614	12.448
S_Creatinine	0.877	1.766
S_T3	1.554	0.528
S_T4	9.878	9.753
S_TSH	2.170	2.804
S_VitD3	32.457	14.325

Table 4 : Avg pretransfusion Hb and sex distribution

	Sex	N	Mean	Median	SD	Minimum	Maximum
Avg_Hb	Female	**29**	**7.97**	**7.90**	**1.416**	**5.80**	**11.40**
	Male	**48**	**7.46**	**7.65**	**0.799**	**5.50**	**8.80**

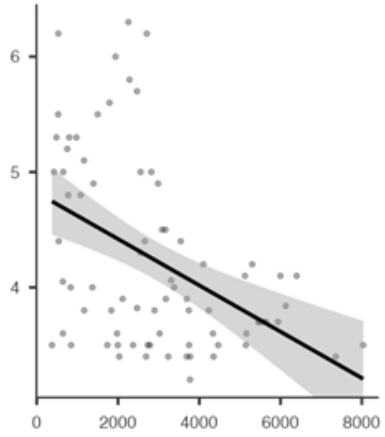
Fig: 2

Correlation between average serum ferritin and various lab parameters were analyzed. Elevated serum ferritin has shown a strong correlation with high levels of liver enzymes. Blood urea has shown some significant correlation with avg serum ferritin but not serum creatinine. There is a significant negative correlation between avg S. ferritin and S. albumin. The high levels of LFT and RFT can be correlated to some extent with elevated serum ferritin, in spite of chelation therapy.

Table 5: Correlation table between Avg S. Ferritin values with different lab parameters

Lab Parameters	Correlation with S. Ferritin (r)		
S_Alb	Pearson's r	-0.447	***
	p-value	< .001	
S_Glob	Pearson's r	0.456	***
	p-value	< .001	
A_G_ratio	Pearson's r	-0.356	**
	p-value	0.001	
AAT	Pearson's r	0.402	***
	p-value	< .001	
AST	Pearson's r	0.548	***
	p-value	< .001	
Bl_Urea	Pearson's r	0.294	**
	p-value	0.01	
S_Vit D 3	Pearson's r	-0.1	
	p-value	0.385	

Fig: 3



This cross sectional study includes 77 transfusion dependent β thalassemia children of both sexes between 2 to 18 years of age.

Table 2 shows age distribution where Age at diagnosis being divided into 3 sub groups , the first sub group being 0-6 months with 51 children affected with a highest percentage of 66.2%, The second sub group being 6-12 months with an involvement of 18 children (23.4%) and last sub group of> 12 months with 8 children (10.4%).

The mean values of liver function test (LFT), renal function test (RFT), Thyroid profile, Serum vitamin D3 are depicted in table 3. Data from the table revealed that mean value of ferritin (ng/ml) is 2918±1826, S.Globulin (gm/dl) : 2±0.92, S.Albumin (gm/dl): 4±0.82, A/G ratio: 3±1.9, ALP(IU/L): 144±71.5, AAT(IU/L): 45±25.8, AST(IU/L): 35±16.8, B. Urea (mg/dl):18±12.4, S.Creatinine (mg/dl): 0.8±1.7, S: T3(pg/ml):1.5±0.5, S:T4(ng/ml): 9.8±9.7, S.TSH (mIU/L): 2.1±2.8, S.VitD3 (ng/ml): 32.4±14.3

High levels of LFT are possibly due to hepatic injury caused by iron overload in thalassemic children. Some investigations have described the proposed mechanism of action but the exact mechanism is still unclear. Hence, further detailed studies should be conducted in order to explore the exact reason behind this in future and to find out the promising correlation in thalassemic children receiving multiple blood transfusions.

Serum ferritin levels were above the potentially cardiotoxic level in 19.1% cases in this study. Hence, its periodic monitoring followed by timely initiation of iron chelation therapy is a must to improve prognosis among the cases.

DISCUSSION:

The present study was designed to evaluate the clinical hematological profile and correlate Serum ferritin with liver function tests, renal function tests, thyroid profile and serum vitamin D3 in Beta thalassemia major children coming regularly for blood transfusionat Red cross transfusion centre, Eluru.

Changes in the liver enzymes lead to excessive destruction of RBC and abnormal globin chain is unable to protect RBC in oxidative stress and results in hepatic cell damage.

Blood transfusions can restore an acceptable amount of red blood cells, making the symptoms of anemia disappear or decrease significantly. However, repeated transfusions have a serious side effect: they lead to iron build-up in the patient's body. The Iron accumulated in organs, becomes poisonous and disrupt the normal functioning of the affected organs (heart attack, fibrosis and cirrhosis of the liver) where iron will interact with hydrogen peroxide and free radicals lead to liver damage and reduce its effectiveness.

Hence average Serum ferritin may be taken into account as a biomarker of iron overload in exposed population.

Excess iron is toxic to many tissues, including the liver, endocrine organ and heart, leading to a series of complications which cause morbidity and mortality in these patients.

As iron deposition in the liver takes place it's functions are affected which are predicted by raised serum globulin, serum albumin, A:G ratio, AAT, AST along with blood urea significantly. In our study, we did find statistically significant correlation between the elevated ferritin levels and some of the lab parameters like liver enzymes and blood urea and negative correlation with serum albumin levels, confirming decreased liver functioning.

Chekir KA et al conducted a study on 56 thalassemic children and determined various metabolic parameters. The study suggested that in beta thalassemia first organ impaired was liver. Plasma thiobarbituric acid reactive substances (TBARS) were significantly raised leading to deranged liver functions. Similar finding were seen by Ameli M et al by study conducted in Iran (2006) where they found that mean serum ALT (Alanine aminotransferase) was significantly high in thalassemic children with high serum ferritin and high transfusion index[4].

Sedigheh Shams et al noted the similar findings from study in Iran with significantly raised liver enzymes (ALT, AST) in homozygous thalassemia major patients than in controls. Asharafsoliman et al observed during a study that some disturbances occur in liver functions in hepatitis negative thalassemia patients with iron overload. Use of Desferroxamine is associated with decrease in liver enzymes. Barton JC et al noted similar results as serum ferritin increases liver enzymes also increases[4].

Saral, Nishtha, et al (2015) found the activities of the liver enzymes in serum (AST, ALT) were significantly higher in beta thalassemic patients as compared to controls, the values were 36.56$\pm$22.05 U/L in ALT and 40 $\pm$ 23.41 U/L in AST. They also observed the value of serum bilirubin level as 0.95 $\pm$0.62 mg/dl[5].

Thalassemia possesses a challenge to health and it drastically reduces the quality of life. However, with optimal treatment the quality of life and life expectancy of these patients can be improved. Other factors in thalassemia that affect growth disorders are decreased level of pre transfusion haemoglobin, high serum ferritin level, suboptimal use of iron chelator and increasing age of thalassemic children.

CONCLUSION:

Thalassemia syndromes are an important cause of morbidity and mortality in children. With increase in number of transfusions, derangement of LFT, RFT and Serum Ferritin has been observed. Oral chelation was not found to be effective in reducing Iron overload. In this study there was a significant correlation between serum ferritin and LFTs. Hence thalassemic children requiring regular blood transfusion need better strategies for removing excess Iron from their body and a larger study may be necessary to find out the exact correlation between Iron overload and high levels of LFT.

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