Original Research Article

Lipid profile in children of β -thalassemia major and their correlation with serum ferritin

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ABSTRACT

Background: β -thalassemia major is a secondary iron load state. The high serum ferritin accounts for abnormal lipid profile. This study was done to investigate the lipid profile in children with β -thalassemia major and to know their correlation with serum ferritin.

Methods: Fifty-five (55) children of beta thalassemia major in the age group of 4-20 years from thalassemia unit of tertiary care hospital who were on regular blood transfusion and oral iron chelators were enrolled. Serum ferritin levels and lipid profile of these children were investigated and their correlation was assessed.

Results: Out of total 55 children 31 (56.4%) children were of female sex and 48(87.3%) were Hindu by religion. The mean rate of blood transfusion was 157.02 ± 21.33 ml/kg/year with average dose and duration of iron chelation with Desferrioxamine was 34.4 ± 26.86 mg/kg /day and 2.34 ± 1.86 years respectively. Mean cholesterol level, high density lipoprotein (HDL), low density lipoprotein (LDL) levels were on lower side of the range with values of 124.47 ± 19.81 mg/dl, 36.58 ± 12.22 mg/dl, 63.94 ± 4.57 mg/dl respectively. The mean triglyceride level (TG) was on higher side with an average of 142.93 ± 33.7 mg/dl. The average serum ferritin levels were 2130.33 ± 859.85 ng/ml. There was negative correlation of total cholesterol, HDL, LDL with serum ferritin with coefficient of correlation ($r = -0.77, -0.55, -0.72$) respectively. The serum triglyceride had positive correlation with serum ferritin with coefficient of correlation ($r = +0.85$).

Conclusions: As the serum ferritin increases, there occurs more derangement of lipid profile in form of decreasing serum cholesterol, HDL, LDL and increasing serum TG levels.

Keywords: Dyslipidemia, Hemoglobinopathy, Serum Ferritin, Thalassemia

INTRODUCTION

Beta thalassemia is an autosomal recessive disorder seen all over the world caused by defect in beta globin chain synthesis of haemoglobin. In individuals with thalassemia there is either complete absence of beta globin production (Beta-Thalassemia major) or partial reduction of beta chain synthesis (beta thalassemia minor).¹ Thalassemia gene is carried by 150 million or 3% of world population with clinically apparent disease only in 15 million

population. one lakh thalassemia children are born every year in world with birth rate of 22.8/10000. In India 10000 thalassemia children are born every year.²

In thalassemia major, individual is unable to make enough healthy haemoglobin and depends on frequent blood transfusions throughout the life. Frequent blood transfusions cause progressive iron overload which is the major complication of treatment. Thalassemia is a secondary iron overload condition. Iron overload is

because of both due to increased absorption of iron from gut and from frequent blood transfusions.³

Liver is the earliest site of iron overload in regularly transfused children and common cause of morbidity. Iron overload occurs both in hepatocytes and reticuloendothelial cells. Iron induced liver injury is characterized by development of fibrosis and eventually cirrhosis. Liver damage in thalassemia major accounts for low serum levels of total cholesterol, high density lipoproteins (HDL) and low density lipoproteins (LDL).⁴

Liver iron is gold standard for determining body iron, though T2 MRI is best non-invasive method of determining liver iron.⁵ Derangement of lipid profile can be taken as indirect evidence of iron overload in liver so this study was planned to investigate the lipid pattern in thalassemia major children and to correlate their levels with serum ferritin.

METHODS

The study was single centre tertiary hospital based prospective correlation study, carried out in thalassemia unit of medical college hospital of south Rajasthan, India. Fifty-five (55) thalassemia major children of 4-20 years who were on regular iron chelation therapy with deferasirox since at least 1 year were taken for study. All children were transfusion dependent at the rate of once or twice a month. These children were seronegative for HIV, HCV and HbsAg and were not having any other significant medical or surgical condition. Thalassaemic children who came for blood transfusion were asked to come empty stomach next time. On next visit blood was obtained in plain vial for serum lipid estimation. Total cholesterol, triglyceride, low density lipoprotein cholesterol, and high density lipoprotein were estimated. HDL was estimated by homogenous enzymatic colorimetric assay. Cholesterol was measured by using the cholesterol oxidase: p-aminophenazone (CHOD: PAP) method. Levels between 5th and 95th percentile for the age and sex were considered normal.

The venous blood was also taken for determination of haemoglobin and ferritin levels for which 2 ml k3 EDTA vial was used. Ferritin level was measured by Elecys 2010 which uses ferritin specific antibody sandwich. Ferritin specific antibodies coats the ferritin. The statistical calculation was done by using ANOVA SSPS software.

RESULTS

Out of total 55 subjects, majority of children 33 (60%) were in the age group of 4-8 years. Only 11 (20%) children were more than 12 years old. Female preponderance was seen in 31 (56.4%) of subjects. Most of the patients belonged to Hindu religion 48 (87.3%) and

rest were Muslims. Mean haemoglobin concentration after blood transfusion was 9.7gm/dl. All basic parameters of subjects were as shown in Table 1. The mean serum ferritin was 2130 ± 859.85 ng/ml. only 3 (5%) patients maintained serum ferritin levels of <1000 ng/ml. Lipid levels at different serum ferritin were as shown in Table 2. Total cholesterol, HDL, LDL levels were declining as serum ferritin was increasing while triglyceride levels were rising as serum ferritin was increasing. Mean values of only LDL were statistically significant (p value 0.001).

Figure 1: Lipid levels at different serum ferritin levels.

The serum cholesterol was on lower side of average 124.47 ± 19.81 mg/dl, HDL was decreased with average of 36.58 ± 12.22 mg/dl while LDL was reduced with mean of 63.94 ± 4.57 mg/dl. Triglyceride was on higher side with average of 142.92 ± 33.70 mg/dl. But at different levels of serum ferritin the cholesterol, HDL, LDL were decreasing while triglyceride levels were increasing as shown in Figure 1.

When serum ferritin levels were correlated with number of blood transfusions, we found that after 30 blood transfusion the serum ferritin increases to a large extent and it continues to rise further, as number of transfusion further increases. The Pearson bivariate coefficient correlation was positive ($r = +0.33$) as depicted in Figure 2.

The Serum cholesterol levels remains in normal range till the serum ferritin levels of 1500 ng/ml. With further increase in serum ferritin levels, rapid fall in serum cholesterol level was seen. Cholesterol levels reaches the lower value of normal (<130 mg/dl) as the serum ferritin levels crosses 1500 ng/ml, which was statistically significant with Pearson's bivariate correlation coefficient of -0.77 as depicted in Figure 3. As the serum ferritin level increases beyond 1500 ng/ml, there was steep increase in serum triglyceride levels. Serum triglyceride levels crosses the upper value of normal (>138 mg/dl) as the serum ferritin reaches the above-mentioned level as depicted in figure 4

Table 1: Basic general variables in thalassemic children.

Variables	Mean	SD
Age (year)	8.8	3.88
Age at diagnosis (in months)	29.91	31.04
No. of blood transfusions	84.65	85.71
Rate of blood transfusion (ml/kg/yr)	157.02	21.33
Dose of deferasirox (in mg/kg/day)	34.4	26.86
Duration of chelation therapy (in years)	2.35	1.87

Table 2: Lipid levels at different S. ferritin levels.

	S. ferritin (ng/ml)	Mean cholesterol (mg/dl)	SD	p -value
1	<1000 (3)	159	21.26	0.02*
2	1000 - <2000 (23)	135.82	19.81	0.18
3	2000 - <3000 (20)	114.85	20.8	0.002*
4	>3000(9)	105.33	20.46	0.001
Mean	2130.33±859.85	124.47	19.81	0.07
	S. ferritin (No)	Mean HDL (mg/dl)	SD	p -value
1	<1000 (3)	53	12.99	0.02*
2	1000 - <2000 (23)	40.91	12.22	0.07
3	2000 - <3000 (20)	33.4	11.99	0.35
4	>3000 (9)	27.1	12.3	0.03
Mean	2130.33±859.85	36.58	12.22	0.75
	S. ferritin (No)	Mean LDL (mg/dl)	SD	p Value
1	<1000 (3)	117.66	28.18	0.001**
2	1000 - <2000 (23)	74.56	24.57	0.001**
3	2000 - <3000 (20)	54.35	24.78	0.45
4	>3000 (9)	40.22	24.1	0.23
Mean	2130.33±859.85	63.94	24.57	0.001**
	S Ferritin (No)	Mean TG (mg/dl)	SD	p Value
1	<1000 (3)	98.66	32.8	0.04
2	1000 - <2000 (23)	122	33.71	0.03
3	2000 - <3000 (20)	152.4	30.57	0.04
4	>3000 (9)	190.11	34.4	0.001**
Mean	2130.33±859.85	142.92	33.7	0.33

*Significant; ** highly significant.

Figure 2: Correlation of serum ferritin with no. of blood transfusion in thalassemic children. **Figure 3: Correlation of total cholesterol with serum ferritin in thalassemic children.**

Figure 4: Correlation of triglycerides with serum ferritin in thalassemic children.

DISCUSSION

Our study shows that serum ferritin levels were abnormally high in most thalassaemic children because thalassemia is secondary iron overload state. This iron overload is mainly due to frequent blood transfusions as there was a positive correlation between number of blood transfusions and serum ferritin ($r=+0.33$).

In the present study, we investigated the lipid pattern in blood of children with β Thalassemia major. It was observed that cholesterol, HDL cholesterol, LDL cholesterol levels were low and triglyceride level were high in regularly transfused thalassemia major children whose serum ferritin levels were >1000 ng/ml. The mean LDL levels were highly deranged ($p=0.001$). There was negative correlation of total cholesterol, HDL, LDL with serum ferritin with coefficient of correlation ($r=-0.77$, -0.55 , -0.72 respectively) while Serum triglyceride had positive correlation with serum ferritin (coefficient of correlation $r=+0.85$).

It appears therefore that many factors such as iron overload (high ferritin level), liver Injury and hormonal disturbance affect lipid pattern among these patients. Liver is the earliest site of iron deposition in regularly transfused thalassemia patients and common cause of morbidity. Iron overload occurs both in hepatocytes and reticuloendothelial cells. Free radical production is increased in patients with iron overload through Fenton reaction. These free radicals accumulate in heart, liver and other organs cause extensive tissue damage.⁶

Mild erythroid hyperplasia also leads to increase removal of LDL by bone marrow. Accelerated erythropoiesis and increased uptake of LDL by macrophages and histiocytosis of reticuloendothelial system are main determinants of low plasma cholesterol levels. Low total cholesterol is caused by hepatic damage and iron overload. Since these changes are signs of lipid peroxidation, the cause of phenomenon was studied.⁷ Papanastasiou et al, had shown that total cholesterol, HDL and LDL cholesterol were significantly decreased while triglycerides were significantly increased in

thalassemia patients as compared to controls. Positive correlation between age and triglyceride was also seen.⁸

Kaltwasser et al noted that increase in triglyceride was observed with increasing ferritin values and positive correlation of patient's triglyceride with both age and oxidative LDL-C antibodies.⁹ Kamal et al noted from a study conducted in Jordan in 2008 that significantly low cholesterol, HDL, LDL were seen as compared to controls.¹⁰ Louis et al observed similar decrease in total cholesterol.¹¹ Patne et al confirmed in their study that lipid abnormality occurs significantly in thalassemia children as compared to controls.¹² Inati et al found during a study conducted in Lebanon that Lipid profile is altered in patients with β -Thalassemia major. Serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels are lower in thalassemia patients than normal controls, while triglycerides (TG) levels were not significantly different or elevated compared to normal controls.¹³ Our study also supports the hypothesis given by previous authors that both serum iron and triglyceride are involved in pathogenesis of LDL cholesterol oxidation. In present study, we elicited significant positive correlation between serum ferritin and triglycerides, a marker of disturbed lipid profile with abnormal iron overload and inadequate chelation.

Limitations of this Study are that most of our patients were poorly chelated, either due to delay in starting chelation or poor compliance and were not maintaining pre-transfusion Hb > 9 gm %.

To conclude, the present study highlights that dyslipidemia occurs in poorly chelated thalassemia major and it further increases as serum ferritin levels increases. Based on this we recommend that every thalassemia patient on regular transfusion but poorly chelated should be screened for dyslipidemia as soon as number of transfusions reach 30 or serum ferritin levels are > 1500 ng/ml. Further studies are needed to assess whether these patients require lipid lowering drugs or not.

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Michel RD, Melissa JF. Elliott. Thalassemia syndrome. In Kleigman RM, Stanton BF, St Geme JW, Behrman RE. Nelson's textbook of Paediatrics. 17th edition. Elsevier publication. 2012;2397-2414.
2. Verma IC, Choudhary VP, Jain PK. Prevention of thalassemia. a necessity in India. Indian J Paediatr. 1992;59:649-54.
3. Richa J, Sachdeva A. Iron overload and its manifestations. In Sachdeva A, Jain R, Aggarwal

- RK, Yadav SP, Broker A. Manual of thalassemia IAP, Pediatric Hemato Oncology. 2009;76-115.
4. Goldfarb A, Rachmilewitz A, Elsemberg S. Abnormal low and high density lipoproteins in homozygous β thalassemia an Italian multicentric study. *Acta Hematol*. 1998;99:76-9.
5. Hillenbra CMR, Loeffler B, Carville M. Evaluation on hepatic iron concentration by T2 MRI in patients with iron overload. *Proc Intl Soc Mag Reson Med*. 2005;105:855-61.
6. Liverea MA, Tesoriere L, Pintaudi AM. Oxidative stress and antioxidant status in beta thalassemia major. Iron overload and depletion of lipid soluble antioxidants. *Blood*. 1996;88(9):3608-14.
7. Scott MD, Eaton JW. Thalassemic erythrocytes. Cellular suicide arising from iron and glutathione dependent oxidation reaction. *Br J Haematol*. 1995;91:811-9.
8. Papanastasiou. Expert panel on detection, evaluation and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA*. 2001;285:2486-97.
9. Kaltwasser JP, Gottschalk. Erythropoietin and iron. *Kidney International Supplements*. 1999;69:49-56.
10. Mansi KM, Aburjaf TA. Lipid profile in Jordian children with β thalassemia major. *UHOD*. 2008;18(2):93-8.
11. Louis CK. Low growth. Growth of children with thalassemia major. *Indian J Paediatr*. 2005;72;159-64.
12. Patne AB, Hisalkar PJ, Gaikwad SB. Lipid abnormalities in patients with beta thalassemia major. *Int J Pharma Sci*. 2012;2(1):106-12.
13. Adlette I, Mohammadhassan A, Noureldine, Mansour A, Abbas HA. Endocrine and bone complications in beta-thalassemia intermedia: current understanding and treatment. *Bio Med Res Int*. 2015;10:1155.

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