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Original article:

Study of assessment of cardiac and hepatic iron overload in thalassemia syndrome cases

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Abstract

Introduction: Chelation therapy has been used to eliminate excess iron. The effective management of thalassemic patients, especially in the paediatric age group, requires optimal monitoring of the toxic effects of both iron overload and excessive chelation therapy. Serum ferritin has been widely used as a surrogate marker and a target ferritin level of 1,000 ng/ml is generally recommended.

Material and methods: This study was conducted in the Department of Pediatrics and Blood Bank of Nanavati Hospital and Research Centre. It is a tertiary care hospital where thalassemic patients receive regular transfusions. Patients aged 13-33 years coming for routine blood transfusions at the Nanavati hospital blood bank and also out-patients coming for regular follow up and receiving transfusions at other blood transfusion centres between November 2011 and November 2012 were included in the study. A detailed history and physical examination were completed for all cases and the findings recorded on a proforma.

Results: Out of 53 cases the average hepatic iron overload over a study period shows that 34% (18) cases have severe hepatic iron overload, 39.6% (21) cases have moderate hepatic iron overload, 17% (9) cases have mild hepatic iron overload and only 9.4% cases have normal hepatic iron status.

Conclusion: Arterial stiffness increases significantly as cardiac iron overload increases but there is no correlation between arterial stiffness and hepatic iron overload. As stiffness index is an indirect measure of CIMT and early atherosclerosis, it also shows and indirect correlation of CIMT with increasing cardiac iron overload. Thus our findings support the hypothesis that iron overload is a risk factor for early atherosclerosis and cardiovascular disease.

Keywords: Chelation therapy, arterial stiffness

Introduction:

Chelation therapy has been used to eliminate excess iron.[1] The effective management of thalassemic patients, especially in the paediatric age group, requires optimal monitoring of the toxic effects of both iron overload and excessive chelation therapy. Serum ferritin has been widely used as a surrogate marker and a target ferritin level of 1,000 ng/ml is generally recommended.[2] However, serum ferritin represents only 1% of the total iron pool, and as an acute phase protein, the levels can be raised in inflammation (e.g. hepatitis) and liver damage, thus decreasing its specificity as a marker of total body iron. [18, 20, 21] Liver iron concentration (LIC) measured with needle biopsy is currently considered the gold standard for the evaluation of siderosis. [3] However, needle biopsy is invasive, not easily repeatable, and the accuracy of the resulting LIC measurement is greatly affected by hepatic inflammation-fibrosis and uneven iron distribution. [4] The liver iron stores represent the total body iron store. The hepatic iron

correlates with total body iron stores when liver biopsy demonstrates the absence of cirrhosis and focal lesions and thus ensures that iron is uniformly distributed within the liver.[5]

Furthermore, it appears that cardiac iron overload, which is the leading cause of death in thalassemia, cannot be predicted from the degree of liver siderosis, probably because of differences in iron kinetics between liver and heart cells and inability of iron chelators to remove iron from heart as rapidly it removed from liver probably due to possible genetic variations of various cardiac ion transport channels. [6, 4] T2* MRI is a method of iron assessment standardised for heart and liver and has the advantages of being non-invasive, reproducible and accurate.[7]

Iron accelerates the onset of atherosclerosis by damaging the endothelium and increasing the intimo-medial thickness of blood vessels. Thus, we decided to assess effects of iron overload on the vascular intimo-medial system (evaluated at the common carotid artery) and correlation of carotid artery intimo-medial thickness with cardiac and hepatic iron stores in Indian thalassemic patients receiving regular blood transfusion and on chelation therapy.

Material and methods:

This study was conducted in the Department of Pediatrics and Blood Bank of Nanavati Hospital and Research Centre. It is a tertiary care hospital where thalassemic patients receive regular transfusions. Patients aged 13-33 years coming for routine blood transfusions at the Nanavati hospital blood bank and also out-patients coming for regular follow up and receiving transfusions at other blood transfusion centres between November 2011 and November 2012 were included in the study. A detailed history and physical examination were completed for all cases and the findings recorded on a proforma.

Results:

Out of 53 cases (recent cardiac T2*MRI) 20.8% (11) cases had severe cardiac iron overload, 32.1% had moderate cardiac iron overload and 47.2% had mild iron overload to normal cardiac iron status.

Out of 53 cases (recent Liver T2* MRI) 39.6% (21) cases have severe hepatic iron overload, 41.5% (22) cases have moderate hepatic iron overload, 9.4% (5) cases have mild liver iron overload and only 9.4% (5) cases have normal liver iron status.

Out of 53 cases, average cardiac overload over a study period shows 18.9% (10) cases have severe iron overload, 35.8% (19) cases have moderate iron overload and 45.3% cases have mild to normal cardiac iron overload status.

Table No.1: Liver iron (T2* MRI, ms) (avg)

Liver iron (T2* MRI, ms) (avg)	No.	Percentage
< 1.4 (severe hepatic overload)	18	34.0%
1.4 to 2.6 (moderate hepatic overload)	21	39.6%
2.7 to 6.2 (mild hepatic overload)	9	17.0%
>= 6.3 (normal)	5	9.4%
Total	53	100.0%

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Out of 53 cases the average hepatic iron overload over a study period shows that 34% (18) cases have severe hepatic iron overload, 39.6% (21) cases have moderate hepatic iron overload, 17% (9) cases have mild hepatic iron overload and only 9.4% cases have normal hepatic iron status.

Table No.2: Correlation between Cardiac T2 * MRI, Liver T2* MRI & various variables in cases

Variables		Cardiac T2* MRI (avg, ms)	Liver T2* MRI (avg, ms)
Serum Ferritin	**Pearson Correlation**	0.089	**-.302(*)**
	p-value	0.52693	0.02812
Mean CIMT (mm)	**Pearson Correlation**	0.066	0.017
	p-value	0.64091	0.90467
Mean Stiffness index	**Pearson Correlation**	**-.292(*)**	-0.188
	p-value	0.03403	0.17683
Mean YEM	**Pearson Correlation**	-0.251	-0.186
	p-value	0.06966	0.18253
Mean RI	**Pearson Correlation**	0.003	0.111
	p-value	0.98294	0.473
Mean PI	**Pearson Correlation**	0.047	0.069
	p-value	0.7639	0.6581
**** Correlation is significant at the 0.01 level (2-tailed).**			
*** Correlation is significant at the 0.05 level (2-tailed).**			

Discussion:

Iron overload in patients with β-thalassemia major may result in systolic and diastolic dysfunction of the left ventricle. Although myocardial parenchymal damage occurs secondary to iron overload, atherogenic vascular complications have also been described in β-thalassemia patients, which has been attributed to an increase in lipid peroxidation mainly caused by highly toxic hydroxyl radicals generated by Haber-Weiss reaction (catalytic role of iron in free radical reaction to produce oxidative stress) with the help of iron [7]. Increased iron stores have been implicated in the association with increased risk of atherosclerosis. [8]

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The other studies such as Y. F. Cheung et al (2006) shows the carotid IMT was significantly greater in patients than controls (0.45 ± 0.04 mm vs. 0.39 ± 0.02 mm, P < 0.001) [9] Cece ve ark. et al (2012) shows CIMT of Right CCA, Left CCA & mean CCA in β-thalassemia patients had significantly greater than controls as mean ± SD (0.47±0.04; 0.47±0.05; 0.47±0.05) & controls (0.40±0.03mm; 0.40±0.04mm; 0.40±0.03mm) respectively with p value p<0.001. [10] Ismail & El-Sherif (2010) study shows that Carotid IMT in the thalassemic patients was significantly increased compared to the normal controls. The mean ± SD of CIMT was (0.46±0.08 and 0.35±0.03 mm) in BTM patients and the controls respectively (p<0.037). [11]

Conclusion:

Arterial stiffness increases significantly as cardiac iron overload increases but there is no correlation between arterial stiffness and hepatic iron overload. As stiffness index is an indirect measure of CIMT and early atherosclerosis, it also shows and indirect correlation of CIMT with increasing cardiac iron overload. Thus our findings support the hypothesis that iron overload is a risk factor for early atherosclerosis and cardiovascular disease.

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