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Original Article

Paediatrics Section

Correlation between Ferritin and Iron Overload in Heart and Liver in Beta-Thalassaemia Major Patients in Shahrekord, Iran

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ABSTRACT

Introduction: Beta-thalassaemia is one of the severe types of thalassaemia with very high healthcare costs. Iron overload in heart and liver is the most fatal complication in beta-thalassemia.

Aim: This study was performed to investigate the correlation between the heart and liver overload and blood ferritin level, Nucleated Red Blood Cells (NRBCs) proportion, and other effective factors involved.

Materials and Methods: In this descriptive-analytical study, 59 thalassaemia major patients were investigated. These patients underwent transfusion 2-3 times a week and were enrolled in the study by convenience, non random sampling. Iron overload in heart and liver was measured by MRI T2*. Furthermore, some variables such as haemoglobin level, transfusion intervals, transfusion rate, spleen size, the type and dose of chelators, and NRBCs as well as demographic variables including age, gender, and race were analysed in this study. The data were analysed by SPSS version 18.

Results: Our study showed that if there was a reduction in NRBCs proportion, ferritin level and liver quantitative iron overload decreased ($p<0.05$) and heart iron overload increased ($p<0.05$). Also, an increment of ferritin level was correlated with an increment of iron overload in heart and liver. Less mean haemoglobin was correlated with decrease in liver iron overload and increase in heart iron overload.

Conclusion: Ferritin could not be constantly used alone as a suitable index of overload in liver and heart in beta-thalassaemia major patients and it is necessary to take the specific conditions of each patient into account and to use other parameters such as haemoglobin and NRBCs proportion besides ferritin.

Keywords: Haemoglobin, Monogenic disorders, Transfusion

INTRODUCTION

Haemoglobinopathies are the most prevalent monogenic disorders in human [1]. Haemoglobinopathies are inherited disorders of haemoglobins that cause change in the structure of haemoglobin or the rate of its synthesis. Thalassaemia syndromes are categorized into alpha, beta, gamma, and sigma and alpha-beta based on the reduced and/or no synthesis of the chain [2,3]. The most prevalent types of thalassaemia are alpha and beta-thalassemia. In beta-thalassemia, there is a reduction in and/or no formation of beta-globulin chain and is manifested as trait beta-thalassemia, beta-thalassaemia intermedia, and beta-thalassaemia major. Beta-thalassaemia major is a severe type of thalassaemia and is associated with stupendous healthcare costs and mortality [4]. Beta-thalassaemia homozygous state is called thalassaemia major. In thalassaemia major, lack of both globin genes leads to a wide range of clinical conditions ranging from transfusion dependence (thalassaemia major) to mild or moderate anemia (thalassaemia intermedia). The reduction in beta chain synthesis in homozygous state leads to accumulation of unstable alpha. The alpha chain accumulation in erythroid precursors causes disturbance in longevity of these precursors and severely ineffective haematopoiesis in bone marrow, leading to severe extramedullary hematopoiesis [5-7].

Transfusion is considered a main treatment for thalassaemia major patients. Haemosiderosis is an inevitable and fatal complication of long term transfusion. The symptoms of iron overload in heart may manifest as deposition in heart (cardiomegaly and heart failure), deposition in endocrine such as diabetes mellitus, hypothyroidism and hypoparathyroidism or growth retardation and hypogonadism, and ultimately liver involvement as fibrosis and cirrhosis [8-11].

MATERIALS AND METHODS

In this descriptive analytical study, 59 thalassaemia major patients referred to Thalassaemia Ward of Hajar Hospital, in Department of Haematology-Oncology in Shahrekord University of Medical Sciences between 2014-2015 years from March to August for six months were studied. All patients suffering from thalassaemia were included in the study and those patients who were not keen to participate were not considered. Out of 65 patients six were excluded from the study.

All patients underwent transfusion 2-3 times a week and were enrolled in the study by convenience, non random sampling. Iron overload in heart and liver was measured by MRI T2. MRI T2 is a technique in which MRI is used to estimate the rate of iron load in heart and was valued by CMR tools software. T2 is a marker to show iron overload in liver and heart.

Liver iron overload was classified into four levels based on MRI2 technique and radiologist reports and the ferretin level was measured by ELISA method: Normal (>3.6 ms), Mild (2.8-3.6 ms), Moderate (2.7-4.1 ms), and Severe (<4.1 ms).

Also heart T2* was divided into-Normal (>20 ms), Mild (14.1-20 ms), Moderate (10-14 ms), and Severe (<10 ms) (28-30).

T2* is a reliable index of iron overload in liver and heart which was evaluated by CMR Tools software. Furthermore, some variables such as haemoglobin level, transfusion intervals, transfusion rate, spleen size, the type and dose of chelators, and nucleated red blood cells (NRBCs) as well as demographic variables including age, gender, and race were analysed.

This project was approved by ethical committee of Shahrekord University of Medical Sciences with No. 1526.

STATISTICAL ANALYSIS

All demographic and baseline data were recorded in a checklist and analysed by SPSS 18. Descriptive data were analysed by Student's t-test and numerical data were analysed by Fisher's exact test and Chi-square test.

RESULTS

The patients had the age range between 3-49 for males, 5-31 for females. Overall mean (standard deviation [SD]) age was 20.15±8.59 years and the age range was approximately similar in male and female patients [Table/Fig-1]. This indicated a similar age and gender distribution in the patients and there was not any correlation between the findings and gender of the patients. [Table/Fig-2] shows descriptive data of liver qualitative iron overload. The highest percentage was obtained for moderate class.

[Table/Fig-3] shows the mean (SD) number of NRBC at different qualitative levels of liver iron overload. As shown, mean NRBC increased in the patients with progression of the disease.

[Table/Fig-4] shows the descriptive data of heart qualitative iron overload.

[Table/Fig-5] shows mean (SD) number of nucleated red blood cells at different qualitative levels of heart iron overload.

[Table/Fig-6] shows the mean (SD) of haemoglobins at different qualitative levels of heart iron overload.

Ferritin level and NRBC proportion, heart quantitative MRI T2* and NRBC proportion, and NRBC proportion and haemoglobin level were positively correlated (p=0.538, 0.296, and 0.264, respectively, p<0.05), indicating a direct relationship between them.

Heart quantitative MRI T2* and NRBC proportion were not significantly correlated (p>0.05), but there was a small

Variables	n	Age minimum	Age maximum	Mean±SD
Male	32	3	49	19.8±10
Female	33	5	31	20.48±7
Total	65	3	49	20.15±8.59

[Table/Fig-1]: Demographic features of the patients.

MRI T2*	N	%
Mild	12	20.33
Moderate	20	33.89
Severe	8	13.55
Normal	19	32.20
Total	59	

[Table/Fig-2]: Descriptive data of liver qualitative iron overload.

Liver qualitative MRI T2*	Mean ± SD	No.
Mild	19/08±27/761	12
Moderate	38/6±27/117	20
Severe	44/63±14/302	8
Normal	7/42±8/809	19

[Table/Fig-3]: Mean (standard deviation) of nucleated red blood cells proportion at different levels of liver qualitative MRI T2*.

MRI T2*	Frequency	%
Mild	14	72.23
Moderate	12	20.33
Severe	4	6.77
Normal	29	49.15
Total	59	100

[Table/Fig-4]: Descriptive data of heart qualitative iron overload.

Heart qualitative MRI T2*	Mean±SD	No.
Mild	25/50±1/317	16
Moderate	24/62±2/987	13
Sev	25/50±2/887	4
Normal	24/97±2/353	29

[Table/Fig-5]: Mean (SD) number of nucleated red blood cells at different qualitative levels of heart MRI T2*.

Liver qualitative MRI T2*	Mean±SD	No.
Mild	24/50±2/195	12
Moderate	25/68±1/937	22
Severe	25/50±2/563	8
Normal	24/55±2/544	20

[Table/Fig-6]: Mean (standard deviation) number of hematocrit at different levels of liver qualitative MRI T2*.

direct relationship between them because the correlation coefficient between them was 0.05.

Liver quantitative MRI T2* and NRBC proportion, heart quantitative MRI T2* and ferritin level, and liver quantitative MRI T2* and ferritin level were negatively correlated (p=-0.421, -0.297, and -0.422, respectively, p<0.01), indicating an inverse relationship between them.

Heart quantitative MRI and haemoglobin level, and heart quantitative MRI T2* and haemoglobin level in the patients were negatively correlated (p=-0.047 and -0.019, respectively, p<0.05), indicating a weak and inverse relationship between them.

DISCUSSION

In this study, we investigated iron overload in liver and heart in the patients with beta-thalassaemia using MRI T2*. Furthermore, some variables such as haemoglobin level, transfusion intervals, transfusion rate, spleen size, the type and dose of chelators, and NRBCs number as well as demographic variables including age, gender, and race were analysed in this study so that after this study these characteristics may be used to estimate iron load in liver and heart in the centers where MRI T2* is not available

In the present study the correlation between liver quantitative MRI T2* and ferritin level was statistically significant (p<0.01), and the correlation coefficient between these two parameters was derived -0.422 that indicated an inverse relationship; in other words, liver quantitative MRI T2* decreased with increase in ferritin level. More clearly, iron load in liver increased with increase in ferritin level.

Also, the correlation between heart quantitative MRI T2* and ferritin level was statistically significant. The correlation coefficient between these two parameters was obtained -0.297 that represented an inverse correlation; in other words, ferritin level decreased with increase in heart quantitative MRI T2*. More clearly, heart iron load increased with increase in ferritin level.

The findings of the previous similar studies have been completely inconsistent and occasionally contradictory. Some studies have reported no correlation between ferritin level and iron overload in liver and heart [12-16]. For example Leung AW et al., studied to assess cardiac MRI and liver iron overload in transfusion-dependent patients concluded that there was no significant correlation between liver iron overload and heart iron overload and also between ferritin serum level and heart iron overload [17].

In di Tucci AA et al., study of iron overload in 27 transfusion dependent thalassaemia patients for whom transfusion was implemented by T2*, there was no correlation between heart iron overload, and liver iron overload and ferritin serum level [18].

Anderson J et al., studied to diagnose iron overload early in heart using T2*, liver iron overload was significantly correlated with heart iron overload and ferritin serum level [19]. In contrast, some studies have concluded that there is a direct correlation between ferritin level and iron overload in heart and liver, which is consistent with our finding in this study. Christoforidis A et al., investigated the correlation of iron accumulation among liver, heart, and pituitary using MRI and concluded that liver iron overload and heart iron overload were significantly correlated [20].

In addition in Anderson LJ et al., study of the effect of venous deferoxamine on iron load deposition in heart using cMRI-T2* in a Caucasian population, 60% of the patients had pathological cardiac T2* and 19.4% had severe iron overload despite normal left ventricular ejection fraction. With no intervention, these patients were likely to be at high risk of cardiomyopathy [21].

Kalantari H, reported 170 thalassaemia major patients referred to thalassaemia ward of a hospital in Isfahan, central Iran in 2009-2010 indicated a significant correlation between liver iron overload and heart iron overload in the patients [22]. These inconsistent and even sometimes opposite findings could be due to a variety of reasons.

Although, ferritin represents the iron reserves in the body cells, since it is a type of protein of acute phase, it may raise falsely in some cases, including infections, malignancies, and inflammations. In contrast some conditions cause decrease in ferritin level, including severe gastrointestinal bleeding, hyperthyroidism, chronic liver diseases such as hepatitis, malnutrition, and food intake disorder in the body.

The method of iron chelators administration contributes to increasing ferritin. In this regard, Mirbehbahani N et al., study compared the ferritin serum level between the thalassaemia major patients administered with subcutaneous desferal and those administered concurrently with venous and subcutaneous desferal and reported that increase in serum ferritin was equal in the two groups of the patients. Therefore, venous desferal at 60-80 mg/kg body weight accompanied with subcutaneous desferal helps to recover the iron overload condition in thalassaemia patients more efficiently [23]. The type of administered chelator is also effective on the rate of iron accumulation and the resulted complications. Another study demonstrated that among the iron chelators, deferiprone had a better effect on cardiac hemosiderosis than deferoxamine and deferasirox. Further the cardiac function was not better after deferoxamine administration although it led to decrease in ferritin [24].

Talaeipoor S, reported deferasirox and deferoxamine combination treatment was found to decrease ferritin serum levels, but this decrease was not more effective compared to treatment with deferoxamine alone [25].

In Kompani F et al., study to compare the effect of deferoxamine and deferoxamine and deferiprone combination on echocardiography parameters in the patients with beta-thalassaemia major, replacing parenteral deferoxamine with a more convenient treatment, oral concurrent administration of deferoxamine deferiprone, did not cause any cardiac complications and the echocardiography parameters to worsen [26].

Some conditions such as exercise help to decrease ferritin and iron overload in organs. Vashtani H et al., study indicated that an aerobic rehabilitation protocol for major thalassaemia patients caused a considerable decrease in iron and ferritin concentration. Therefore, practicing such exercises within a physiologically safe range, concurrent with transfusion and desferal administration, moderates the adverse effects of iron overload on heart and therefore cardiovascular function improves [27].

Some studies have argued for other factors, rather than ferritin, as being involved in incidence of heart problems, including anemia severity and the age at onset of treatment with deferoxamine. For example Bazrgar M et al., concluded that since there was no significant correlation between ferritin and echocardiography parameters, ferritin level could not be considered as an index of iron level in heart. In this study the patients with more severe anemia and those beginning to take deferoxamine at older ages were more predisposed to left ventricular problems [28].

Ferritin levels are is also correlated with gender and age. Ferritin level is high at birth, then decreases over time, and remains constant in childhood. After puberty, ferritin level begins to increase, which is more notable in men than women. Ferritin level is lower in women because of menstrual bleeding and begins to increase during menopause.

All together, it could be inferred that the ferritin level alone could not be used to estimate iron overload in liver and heart and other variables that are directly or inversely correlated with iron overload in heart and liver, including haemoglobin level and NRBC proportion, should be considered. In the present study, ferritin level increased with increase in NRBC. Furthermore, liver iron overload increased with increase in NRBC proportion.

In addition although the correlation between heart iron overload and haemoglobin level in the patients was not statistically significant and the correlation coefficient between them was approximately zero, this small correlation indicated an inverse relationship; in other words, haemoglobin level decreased with increase in quantitative MRI T2*.

In other words, iron overload and mean haemoglobin level were directly correlated. The only explanation for this finding is that higher haemoglobin in the patients could represent higher transfusion and therefore increased iron overload to which heart iron overload is secondary. However, this correlation is statistically small and deserves further investigations.

Although, the correlation between liver iron overload and haemoglobin level was not statistically significant and the correlation coefficient between these two parameters was approximately zero from a statistical point of view, the smaller (-0.019) correlation between them represented a weak, inverse relationship. In other words, haemoglobin decreased with increase in liver quantitative MRI T2*. More clearly the lower the mean haemoglobin level is, the lower iron load in liver is.

Another finding in the present study was the statistically significant and direct correlation between NRBC proportion and haemoglobin level in the patients. In other words, haemoglobin increased with increase in NRBC and vice versa.

In the present study, as NRBC proportion increased, iron overload increased in liver and decreased in heart. To the best of our knowledge, no consistent or inconsistent study with this finding has been yet conducted, which necessitates further studies. However this finding could be explained by the increase in NRBC being representative of severity of bone marrow activity and hence increased gastrointestinal absorption and furthered liver deposition of iron. According to this study, it is suggested that for evaluation, the rate of Iron in liver and heart along with Ferritin, NRBC and patient's Hb level should be considered.

LIMITATION

Patients in the current study were not in high numbers. If this study was conducting on more patients, the results were more accuracy.

CONCLUSION

Although ferritin is a sensitive index to examine the body iron reserves, it could not be constantly used alone as a suitable index of overload in liver and heart in beta-thalassaemia major patients and it is necessary to take the specific conditions of each patient into account and to use other parameters such as haemoglobin and NRBC proportion besides ferritin.

It is recommended to provide required conditions to take diagnostic measures for early diagnosis and intervention in iron overload in the vital tissues using the modern technique MRI T2*. Furthermore since the present study indicated that in addition to ferritin, other indexes such as haemoglobin and NRBC proportion could greatly assist in early diagnosis of iron overload in the body's vital tissues, it is recommended that the above parameters be also measured at clinical level. Similar studies with larger sample size and/or other ethnicities and comparison of their findings with the present study are recommended.

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