Pediatrics & Therapeutics

Sarhan et al., Pediatr Ther 2017, 7:3
DOI: 10.4172/2161-0665.1000324

Research Article OMICS International

Magnetic Resonance Imaging Versus Serum Ferritin Levels in Detection of Liver and Cardiac Iron Overload in Non-Transfusion Dependent Thalassemia

Mohamed Mahmoud Sarhan[1], Mohamed Mohamed El-Asmy[1], Eman Muhammad Abdelsalam[2*] and Ghada Magdy Mohamed[1]

[1]*Department of Pediatrics, Mansoura University, Egypt*

[2]*Department of Radiodiagnosis, Mansoura University, Egypt*

[*]**Corresponding author:** Eman Muhammad Abdelsalam, Department of Radiodiagnosis, Mansoura Faculty of Medicine, Mansoura University, Egypt, Tel: 971543462504; E-mail: emanmohammad.em@gmail.com

Received date: Jun 13, 2017; **Accepted date:** Jul 10, 2017; **Published date:** Jul 12, 2017

Abstract

Background: MRI is now established as the non-invasive modality of choice for the diagnosis of liver iron overload. Recently, it has been used to estimate myocardial iron overload in adult patients with acquired anemia.

Objective: To assess the value of gradient-echo T2* in monitoring and screening of both liver and cardiac iron overload in non-transfusion dependent thalassemia (NTDT).

Material and methods: This prospective study was conducted on children with mean age 11 years. Measurements were obtained in the same 1.5 MRI examination, followed by calculation with the reference spread sheet and then, the results were compared to the standard serum ferritin levels.

Results: The study included 31 patients with non-transfusion-dependent thalassemia (NTT); 19 with thalassemia-intermedia, 6 with thalassemia-minor and 6 with hemoglobin-H. Mean serum ferritin was 201.8 ng/mL. Mean liver T2* was measured at 23.7 ms. Mean myocardial T2* was measured at 30 ms. Correlation analysis revealed significant negative correlation between hepatic T2* and serum ferritin (P<0.001*, R=-0.8). Week positive correlation was found for cardiac T2* (P=0.04, r=-0.37) and a week negative correlation was between hepatic and cardiac T2* values (P=0.4, R=-0.37). Statistically significant negative correlation with age was detected for hepatic T2* (P=0.001, R=-0.44) but not for cardiac T2* and serum ferritin.

Conclusion: Liver and cardiac T2* measurement is the non-invasive modality of choice for monitoring and screening of both liver and cardiac iron overload in NTDT. From our experience, cardiac iron overload is uncommon in this disease population even in cases with mild and moderate hepatic overload.

Keywords: Gradient-echo T2*; Non-transfusion dependent thalassemia; Liver iron concentration; Myocardial iron concentration

Introduction

Thalassemia is the most common genetic disorder worldwide [1]. Non-transfusion dependent thalassemia (NTT) includes a variety of phenotypes, most commonly investigated forms are: β-thalassemia intermedia, β-thalassemia minor and α-thalassemia intermedia (hemoglobin H disease). Unlike β-thalassemia major, regular transfusion therapy is not mandatory for patients' survival [2].

For these patients, iron overload resulting from increased intestinal iron absorption represents an important clinical problem which progresses with age [3]. Serum ferritin is a well-known marker for indirect measurement of iron overload; however its concentration is affected by other factors, e.g. inflammation, chronic disorders and liver diseases [4]. Liver biopsy is another essential diagnostic tool for the estimation of the extent of iron deposition in the hepatic lobules; however, being an invasive technique, it carries the risk of post-interventional complications e.g. bleeding. Also, it cannot assess the overall iron burden within the whole organ [5].

Iron chelation therapy is used for management of non-transfusion dependent thalassemia after the age of ten (more than fifteen years in deletional hemoglobin H phenotype). It is indicated when iron concentration reaches 5 mg Fe/g or over dry weight; or when serum ferritin level exceeds 800 ng/mL because these thresholds carry the risk of iron-overload related morbidity [6].

Early diagnosis of cardiac iron overload is mandatory, as it requires intensified chelation treatment; otherwise irreversible heart failure could be inevitable [7]. Yet, usually the diagnosis is delayed because cardiac iron overload is unpredictable, symptoms and abnormal echocardiographic results appear late [1].

MRI is now established to be a reliable non-invasive modality for the diagnosis of liver iron overload [8,9]. This is owing to the high sensitivity of multi-echo gradient T2* sequences to the excess tissue iron. Quantitative assessment is achieved by fitting the appropriate decay model to the average signal intensity at various echo times, where tissue iron overload has magnetic susceptibility effect that cases the signal decay due to shortening of T2 time constant [10]. Recently, it has also been used to estimate myocardial iron overload in adult

patients with acquired anemia. Gradient-echo T2* can rapidly assess cardiac iron overload in the same session of liver iron evaluation [11].

Therefore, the objective of this study was to assess the value of gradient-echo T2* in monitoring and screening of both liver and cardiac iron overload in non-transfusion dependent thalassemia. Measurements were obtained in the same 1.5 MRI examination, followed by calculation with the reference spreadsheet and then, the results were compared to the standard serum ferritin levels.

Material and Methods

Patients

This observational cross-sectional prospective study was carried out in the period between April 2015 and August 2016 in the University Children's Hospital and Magnetic resonance imaging (MRI) unit of Radiodiagnosis department. The study included children with mean age 11 years (ranged from 4 to 18 years), who suffered from non-transfusion dependent thalassemia (NTDT) attending or on follow-up in hematology outpatient clinic. The study was conducted after IRB approval as well as informed consent taken from legal guardians and assent from the older children (more than 12 year).

Detailed history and data including age, sex, and duration of illness, history of blood transfusion, affected parents or other affected siblings were recorded. Physical examination was carried out with special emphasis on complexion, growth parameters, and stage of puberty, size of the liver and spleen and presence of characteristic facies, splenectomy or cholecystectomy.

Serological study

Basic laboratory investigations were documented and confirmed including CBC, reticulocytic count, serum bilirubin (total and direct), serum ferritin (at the time of study), liver function tests, serum calcium, phosphorus and alkaline phosphatase, chest x-ray and abdominal ultrasound (at the time of study).

Imaging

MR imaging was obtained by using a 1.5-T, whole-body scanner (Acheiva; Philips Medical Systems, Best, Netherlands). Initial morphological T1 weighted sequences were carried out followed by axial gradient echo breath-hold multiecho T2* sequences; acquired with electrocardiogram synchronization. The parameters were as follows: TR/TE1/delta TE, 19/2.1/1.4, followed by echo train of 12 echo times from 2.2 to 19.3 milliseconds; flip angle 20 degrees; slice thickness, 10 mm; interslice gap, 2 mm; matrix size, 256 × 128; field of view, 350 × 350 × 10 mm; number of signals acquired, 1; acquisition time, 13 seconds.

Post processing and data analysis

Regions of interest (ROIs) of fixed area were placed in the liver parenchyma, clear of the hepatic veins and biliary tree, to measure the signal intensity of the affected hepatic segments (Figure 1). For cardiac T2* assessment, ROI was placed in the interventricular septum in all images, encircling both epicardial and endocardial regions, but away from the right ventricular insertion points (to avoid artifacts) (Figure 2).

To create exponential decay curves TE and SI values were manually inserted into the Excel sheet where SI (y-axis) is plotted against TE (x-axis) to make a graph (Figures 1 and 2). Truncation of data was achieved by excluding points where SI was very low (flat).

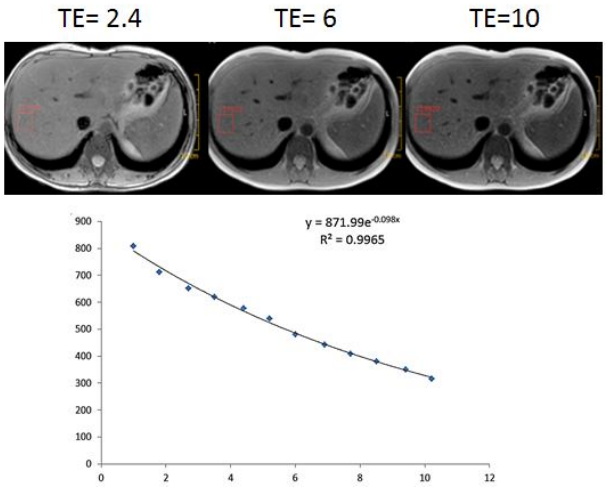

Figure 1: Calculation of liver T2* value in miliseconds plotted against signal intensity obtained from axial images at 12 increasing TEs, with fitting of monoexponential decay curve. In this case TE was 10.2 ms and LIC was 3.02 mg/g; denoting moderate iron overload.

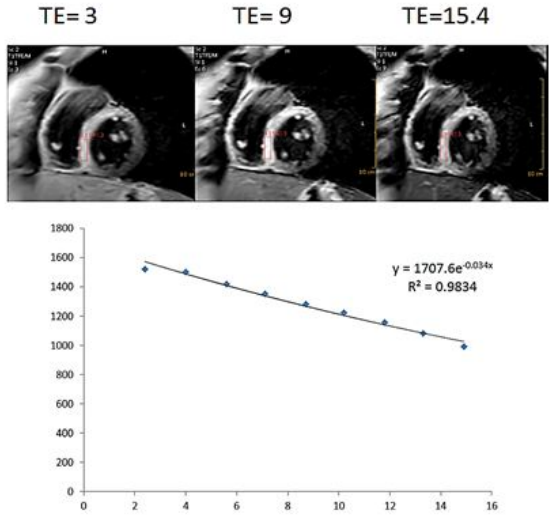

Figure 2: Calculation of myocardial T2* values obtained from short-axis images at 16 increasing TEs. In this case TE was 29.3 ms and MIC was 0.73 mg/g; denoting normal T2* value.

Statistical data analysis

Results are presented as mean ± SD or median (minimum-maximum). Spearman correlation, age and gender-related analysis

were done. The statistical procedures were performed with SPSS statistical software v20 (SPSS, Inc., Chicago, IL, USA).

Results

The study included 31 patients with non-transfusion dependent thalassemia (NTT); 19 with thalassemia intermedia, 6 with thalassemia minor and 6 with hemoglobin H. Mean serum ferritin was 201.8 ng/mL (median 112.6; 9 ng/mL min and 663 ng/mL max). Mean liver T2* was measured at 23.7 ms (median 25; 3.2 ms min and 44 ms max). Mean myocardial T2* was measured at 30 ms (median 29 ms; 19.9 ms min and 67 ms max). These values are corresponding to mean liver iron concentration (LIC) 2.6 mg/g ± 3.8 SD; 0.69 min, 20.4 max and mean myocardial iron concentration (MIC) 0.75 mg/g ± 0.23 SD; 0.27 min, 1.17 max.

The mean, median values and ranges of serum ferritin and T2* values of the liver and cardiac iron concentrations for the 3 phenotypes of NTDT are shown in Tables 1 and 2.

Thalassemia Trait	Serum ferritin (in ng/mL) Mean Median	Min-max
Thalassemia intermedia	230.14 174.0	35.4-663.0
Thalassemia minor	133.9 61.5	9.1-541.4
Hb-H	179.7 106.8	62.3-613.0

Table 1: Serum ferritin in the 3 NTDT traits.

Organ	Thalassemia trait	Median T2* (in milliseconds)	Minimum to maximum
Liver	Thalassemia intermedia	23.8	3.2-44.0
	Thalassemia minor	32.25	8.5-42.0
	Hb-H	30.8	3.4-41.5
Heart	Thalassemia intermedia	29.3	19.9-67.1
	Thalassemia minor	26.8	22-34.8
	Hb-H	30.35	22.2-40.6

Table 2: T2* values of liver and myocardial iron concentration in the 3 NTDT traits.

Variables	Pearson correlation (P)	Correlation co-efficient (r)
T2*liver/serum ferritin	<0.001*	-0.8
T2*heart/serum ferritin	0.04**	0.37
T2*liver/ T2*heart	0.04**	-0.4
* Correlation is significant at the 0.01 level (2-tailed). ** Correlation is significant at the 0.05 level (2-tailed).		

Table 3: Correlation analysis for T2* values.

Four cases of thalassemia intermedia and one case with thalassemia minor trait showed increase in liver T2* values (8.1, 10.2, 10.4, 5.4 ms and 8.5 ms) corresponding to LIC 3.85, 3.02, 3, 5.7 and 3.63 mg/g, respectively. This was reported as mild liver iron overload, its threshold is T2* 3.8-1.14 ms, LIC 2-7; according to Garbowski et al. [12].

One case with thalassemia intermedia and one case with Hb-H showed increase in liver T2* values (3.2 and 4.4 ms) corresponding to LIC 9.8 and 11.7 mg/g, respectively. Moderate liver iron overload threshold is T2* 1.8-3.8 ms, LIC 7-15 mg/g [12].

Three cases with thalassemia intermedia were recorded as high normal T2* values 19.9, 19.9 and 20.1 ms, corresponding to 1.17, 1.17 and 1.08 mg/g, respectively. Mild myocardial iron overload threshold is 15-20 ms, MIC 1.16-1.65 mg/g; according to Carpenter et al. [13]. Meanwhile, none of the recorded myocardial T2* values was beyond the pathological threshold.

Variables	Pearson correlation (P)	Correlation coefficient (r)
T2* liver/age	0.01*	-0.44
T2* heart/age	0.52	0.11
Serum ferritin/age	0.07	0.32
* Correlation is significant at the 0.01 level (2-tailed). ** Correlation is significant at the 0.05 level (2-tailed).		

Table 4: Correlation of T2* values and serum ferritin with age.

Correlation analysis revealed significant negative correlation between hepatic T2* and serum ferritin. In contrast, a week positive correlation was found for cardiac T2* and a week negative correlation was between hepatic and cardiac T2* values (Table 3).

A statistically significant negative correlation with age was detected for hepatic T2* but not for cardiac T2* and serum ferritin (Table 4). Gender related analysis revealed no significant statistical correlation for serum ferritin and T2* values with sex.

Discussion

In thalassemia, iron overload results from both elevated gastrointestinal absorption and transfusion therapy [14]. In non-transfusion dependent thalassemia (NTDT), iron overload is primarily due to gut absorption. Despite the fact that transfusion dependence may develop with age, organ failure and death are far less common as compared with severe forms of thalassemia [15].

Although numerous studies have confirmed MRI as the method of choice for tissue iron assessment in thalassemia major and transfusion dependent traits, only a few studies were conducted on NTT traits [16-18].

In our study 5 cases (16%) showed mild liver iron overload and 2 cases (6.5%) showed moderately elevated liver iron concentration. All other cases (77.5%) had T2* values within the normal range. Hepatic T2* values significantly correlated with serum ferritin and with patients' ages (Tables 3 and 4). These findings are in agreement with previous studies which reported that although serum ferritin correlated with LIC, it was found to be a poor predictor of LIC [17,18]. They explained this to be probably related to a portal first pass effect, less use of iron chelation therapy and older age of patients as compared with severe forms of transfusion dependent thalassemia.

Our results showed that all T2* values were within the normal range (Table 2). No significant correlation was found between myocardial T2* and serum ferritin and week correlation was found between hepatic and cardiac T2* values (Table 3). A previous study stated that marked discordance was found between hepatic and cardiac iron overload as well as myocardial T2* and serum ferritin in a large study cohort comprising 106 patients with thalassemia major [19]. Similarly, studies conducted on thalassemia intermedia trait reported the absence of cardiac iron overload despite hepatic iron accumulation [16,20,21].

These findings are in agreement with previous studies which reported that thalassemia intermedia trait is less prone to develop cardiac overload than thalassemia major (15,18). A study conducted on animal models for iron overload in thalassemia intermedia also indicated the early hepatic iron accumulation and delayed cardiac iron accumulation over longer periods of time [22].

Meanwhile, other studies reported cardiac T2* values above the pathologic threshold in thalassemia intermedia patients who were regularly transfused and on iron chelation therapy [16,17]. Accordingly the existence of factors like transfusion history, chelation therapy or co-pathology has an impact on the location and extent of cardiac iron accumulation [23,24]. Therefore, it is recommended that the decision for the start and regimen of chelation therapy should be spared for older age group patients with regular transfusion, cardiac hemosiderosis or liver fibrosis [17].

Conclusion

In conclusion, liver and cardiac T2* measurement is the non-ivasive modality of choice for monitoring and screening of both liver and cardiac iron overload in NTDT. From our experience, cardiac iron overload is uncommon in this disease population even in cases with mild and moderate hepatic overload.

We recommend further investigation on NTDT on a wider scale and the inclusion of functional cardiac MRI assessment. A threshold value of LIC that could be associated with cardiac overload may be appreciated and should be sought.

References

1. Pepe A, Positano V, Santarelli MF, Sorrentino F, Cracolici E, et al. (2006) Multislice multiecho T2* cardiovascular magnetic resonance for detection of the heterogeneous distribution of myocardial iron overload. J Magn Reson Imaging 23: 662-668.
2. Musallam KM, Rivella S, Vichinsky E, Rachmilewitz EA (2013) Non-transfusion-dependent thalassemias. Haematologica 98: 833-844.
3. Taher A, Hershko C, Cappellini MD (2009) Iron overload in thalassaemia intermedia: Reassessment of iron chelation strategies. Br J Haematol 147: 634-640.
4. Chirico V, Rigoli L, Lacquaniti A, Salpietro V, Piraino B, et al. (2015) Endocrinopathies, metabolic disorders, and iron overload in major and intermedia thalassemia: Serum ferritin as diagnostic and predictive marker associated with liver and cardiac T2* MRI assessment. Eur J Haematol 94: 404-412.
5. Schwenzer NF, Machann J, Haap MM, Martirosian P, Schraml C, et al. (2008) T2* Relaxometry in liver, pancreas, and spleen in a healthy cohort

of one hundred twenty-nine subjects-correlation with age, gender, and serum ferritin. Invest Radiol 43: 854-860.

6. Musallam KM, Cappellini MD, Taher AT (2013) Iron overload in β-thalassemia intermedia: An emerging concern. Curr Opin Hematol 20: 187-192.
7. Ernst O, Thuret I, Petit P, Ameur F, Loundou AD, et al. (2013) Iron overload of hematological origin: validation of a screening procedure for cardiac overload by MRI in routine clinical practice. Diagnostic and interventional imaging 94: 601-608.
8. Gandon Y, Olivie D, Guyader D, Aube C, Oberti F, et al. (2004) Non-invasive assessment of hepatic iron stores by MRI. The Lancet 363: 357-362.
9. Pierre TG, Clark PR, Chua-anusorn W, Fleming AJ, Jeffrey GP, et al. (2005) Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. Blood 105: 855-861.
10. Westwood M, Anderson LJ, Firmin DN, Gatehouse PD, Charrier CC, et al. (2003) A single breath-hold multiecho T2* cardiovascular magnetic resonance technique for diagnosis of myocardial iron overload. J Magn Reson Imaging 18: 33-39.
11. Di Tucci AA, Matta G, Deplano S, Gabbas A, Depau C, et al. (2008) Myocardial iron overload assessment by T2* magnetic resonance imaging in adult transfusion dependent patients with acquired anemias. Haematologica 93: 1385-1338.
12. Garbowski MW, Carpenter JP, Smith G, Roughton M, Alam MH, et al. (2014) Biopsy-based calibration of T2* magnetic resonance for estimation of liver iron concentration and comparison with R2 Ferriscan. J Cardiovasc Magn Reson 16: 40.
13. Carpenter JP, He T, Kirk P, Roughton M, Anderson LJ, et al. (2011) On T2* magnetic resonance and cardiac iron. Circulation 123: 1519-1528.
14. Kremastinos DT, Tiniakos G, Theodorakis GN, Katritsis DG, Toutouzas PK (1995) Myocarditis in β-thalassemia major: A cause of heart failure. Circulation 91: 66-71.
15. Cohen AR, Galanello R, Pennell DJ, Cunningham MJ, Vichinsky E (2004) Thalassemia. Hematology Am Soc Hematol Educ Program 2004: 14-34.
16. Fragasso A, Ciancio A, Mannarella C, Gaudiano C, Scarciolla O, et al. (2011) Myocardial iron overload assessed by magnetic resonance imaging (MRI) T2* in multi-transfused patients with thalassemia and acquired anemias. Eur J Intern Med 22: 62-65.
17. Au WY, Lam WM, Chu WW, Tam S, Wong WK, et al. (2009) Organ-specific hemosiderosis and functional correlation in Chinese patients with thalassemia intermedia and hemoglobin H disease. Ann Hematol 88: 947-950.
18. Pakbaz Z, Fischer R, Fung E, Nielsen P, Harmatz P, et al. (2007) Serum ferritin underestimates liver iron concentration in transfusion independent thalassemia patients as compared to regularly transfused thalassemia and sickle cell patients. Pediatr Blood Cancer 49: 329-332.
19. Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, et al. (2001) Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J 22: 2171-2179.
20. Origa R, Barella S, Argiolas GM, Bina P, Agus A, et al. (2008) No evidence of cardiac iron in 20 never-or minimally-transfused patients with thalassemia intermedia. Haematologica 93: 1095-1096.
21. Roghi A, Cappellini MD, Wood JC, Musallam KM, Patrizia P, et al. (2010) Absence of cardiac siderosis despite hepatic iron overload in Italian patients with thalassemia intermedia: An MRI T2* study. Ann Hematol 89: 585-589.
22. Gardenghi S, Marongiu MF, Ramos P, Guy E, Breda L, et al. (2007) Ineffective erythropoiesis in β-thalassemia is characterized by increased iron absorption mediated by down-regulation of hepcidin and up-regulation of ferroportin. Blood 109: 5027-5035.
23. Papakonstantinou O, Alexopoulou E, Economopoulos N, Benekos O, Kattamis A, et al. (2009) Assessment of iron distribution between liver, spleen, pancreas, bone marrow, and myocardium by means of R2 relaxometry with MRI in patients with β-thalassemia major. J Magn Reson Imaging 29: 853-859.
24. Wood JC (2007) Magnetic resonance imaging measurement of iron overload. Curr Opin Hematol 14: 183-190.