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Original Research Article

Estimation and quantification of liver iron concentration by magnetic resonance imaging

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ABSTRACT

Background: Liver iron overload is considered to be the histological hallmark of genetic hemochromatosis. The accurate estimation of iron overload is important to establish the diagnosis of hemochromatosis. The aim of the present study was to estimate T2* liver value, quantify liver iron concentration (in milligram of iron per gram dry weight) and find out the appropriate therapy for patients with iron overload according to severity index.
Methods: A cross-sectional observational study was carried out in Department of Radio Diagnosis, at B.Y.L. Nair Hospital and medical college, Mumbai from June 2017 to August 2018. A total of 50 cases were enrolled for the present study.
Results: Male predominance (66.0%) was seen. Mean duration of disease among the studied cases was 10.52±6.06 years, with minimum and maximum duration of disease of 1 and 26 years respectively. Eight percent had compliance to visit and treatment among the enrolled cases.
Conclusions: MRI was concluded to be potentially useful non-invasive method for evaluating liver iron stones in a wide spectrum of haematological and liver diseases.

Keywords: Estimation and quantification, Liver iron concentration, Iron overload, Magnetic resonance imaging

INTRODUCTION

Iron is needed by all cells in the human body, particularly cells which produce myoglobin and haemoglobin. However, excess iron accumulation promotes the formation of toxic oxygen radicals which leads to the damage of cells.[1] Iron can accumulate in the liver in a wide variety of conditions such as hereditary hemochromatosis (HH).[2] Hemochromatosis is an iron overload disorder in which a person absorbs too much iron from the food and drink they consume. If left untreated, it can damage various organs in the body. The skin takes on a bronze color. HH can also lead to cancer and heart disease in patients.[3] The presence of iron in tissue in the form of ferritin and hemosiderin, affects the magnetic resonance imaging (MRI) signal and shortens the relaxation times, T2*, T2 and T1. T2 relaxation (T2* value) is the process by which the transverse components of magnetization (Mxy) decay or dephase and is related to the amount of spin-spin interaction that takes place. Free water contains small molecules that are relatively far apart and move rapidly and therefore spin-spin interactions are less frequent and T2 relaxation is slow (leading to long T2 relaxation times). Water molecules bound to large molecules are slowed down and more likely to interact, leading to faster T2 relaxation and shorter T2 relaxation times. Water-based tissues with a high macromolecular content (e.g., muscle) tend to have

shorter T2 values. In cases of iron overload, the deposited iron in the myocardium, results in reduction of the T2 relaxation time. Several studies have accessed liver iron deposition by measuring liver T2* and have revealed liver iron overload in almost all patients.[4,5] Iron overload is considered to be the histological hallmark of genetic hemochromatosis and transfusional hemosiderosis and can occur in chronic hepatopathies.[6,7] Iron homeostasis in patients exclusively modulates iron absorption since, iron excretion is passive (by shedding of intestinal and skin cells) and it cannot be actively regulated.2 Excess iron is toxic because it generates free radicals and induces oxidative stress.[8]

The accurate estimation of iron overload is important to establish the diagnosis of hemochromatosis and guide the chelation treatment in transfusion dependent anaemia.[9,10] In the past 20 years, MRI has emerged as a promising method for measuring liver iron content (LIC) in a variety of diseases. The quantitative measurement of liver iron content provides prognostic information regarding the risk for developing complications such as hepatic fibrosis and cirrhosis. In HH, liver iron quantification is used to identify individuals suitable for phlebotomy therapy and to monitor response to therapy. The role of MRI in LIC determination is important in conditions characterized by iron overload, namely, thalassemia major, other hemoglobinopathies, acquired anaemia and hemochromatosis. This could help in early diagnosis, categorisation and prompt treatment or change in treatment modalities among cases with iron overload.

The aim of the present study was to estimate T2* liver value, quantify liver iron concentration (in milligram of iron per gram dry weight) and find out the appropriate therapy for patients with iron overload according to severity index.

METHODS

A cross-sectional observational study was carried out with 50 cases, in Department of Radio Diagnosis, at B.Y.L. Nair Hospital and medical college, Mumbai from June 2017 to August 2018. All patients were referred from hematology clinic for MRI scan which is a part of their routine clinical management for the present study. The study was approved by the institutional ethical review board and patients with MRI scan results and detailed medical records were included in the study. Around 4 to 5 patients are referred for liver MRI per month in the research site as per the past records.

All patients who are at high risk of iron overload (for e.g., primary hemochromatosis, severe chronic hemolysis of any cause, multiple frequent blood transfusions, either whole blood or red blood cells etc.,) who have been referred for liver MRI and agreeing to consent for the study were included in the present study. Patients not consenting for the study, patients with intracranial aneurysm clips (unless the referring physician is certain that it is made of non-ferromagnetic material such as titanium), intra-orbital metal fragments, patients with any electrically, magnetically or mechanically activated implants (including cardiac pacemakers, biostimulators, neurostimulators, cochlear implants and hearing aids), pregnant female patients (risk versus benefit ratio to be assessed) and patients who are claustrophobic were excluded from the study.

With α of 0.05, β of 0.20 (power of 80%), using reference value of 5.30±4.29 ms (n=60) of MRI T2* value, using below mentioned formula, the sample size was calculated 17.675. However, since sample size of 17.675 was not enough for most statistical analysis, and since resources like patients, investigative tools, time for research existed in sufficient quantity. 50 cases were enrolled for the present study.

$$n = \frac{Z\sigma}{E}$$

where, value from standard normal distribution reflecting CI (Z=1.96 for 95%); standard deviation of the outcome variable and desired margin of error.

The data collected included demographic data as age, gender and address, known case of primary haemochromatosis or thalassemia and severe chronic hemolysis etc., blood transfusions received or not; chelation drug (with dose) or any other drugs and pulse and blood pressure, serum ferritin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), ejection fraction determined by 2D echo and blood sugar.

Statistical analysis

Data was entered in Microsoft Excel and uploaded in Public Safety Partnership Project (PSPP) statistical software for analysis. Qualitative data was represented in form of frequency and percentage. The results were analysed as Chi-square and p values.

RESULTS

Age distribution among enrolled cases indicated a predominance of adolescent cases with 34(68.0%) cases being aged 7 to 16 years and 8(16.0%) aged 17 to 26 years, together accounting for 84% cases. Male predominance (33 cases; 66.0%) was seen among the cases enrolled, demonstrating a known finding that men are significantly more likely to develop hemochromatosis than women.

Almost 50% cases of enrolled cases had been suffering from condition which was likely to cause iron overload for 5 to less than 10 years. Nine (18.0%) cases were having disease for 15 to 19 years. This coincides well with the age distribution of cases.

Mean duration of disease among the studied cases was 10.52±6.06 years, with minimum and maximum duration of disease of 1 and 26 years respectively. Eight percent (40 cases) had compliance to visit and treatment among the enrolled cases.

Biochemical variables like SGOT, SGPT, blood sugar, serum ferritin, 2D echo and ejection fraction were assessed among the enrolled 50 cases, to gauge possible damage to various systems due to iron overload. The biggest derailment appeared in serum ferritin with 94.0% (47 cases) having high serum ferritin, followed by SGPT rise in 35 cases (70.0%) and high SGOT in 29 cases (58.0%). Least alteration was found in fasting blood sugar (FBS) level which was high in only 11 cases.

Table 1: Demographic characteristics among the cases (n=50).

Demographic characteristics	No.	%
Age (in years)		
7 to 16	34	68.0
17 to 26	8	16.0
37 to 46	4	8.0
47 and more	4	8.0
Sex		
Female	17	34.0
Male	33	66.0
Known condition		
Thalassemia major	40	80.0
Thalassemia minor	3	6.0
Sickle cell anaemia	3	6.0
Myelodysplastic syndrome	3	6.0
Primary haemochromatosis	1	2.0
Duration of disease (in years)		
<5	7	14.0
5 to 9	24	48.0
10 to 14	6	12.0
15 to 19	9	18.0
20 and more	4	8.0
Variables		
Serum ferritin high	47	94.0
SGPT high	35	70.0
SGOT high	29	58.0
2D echo ejection fraction reduced	19	38.0
Fasting blood sugar high	11	22.0

MRI T2* value (msec) in liver was estimated for all 50 cases. Based on the categorization, 26 cases (52.0%) had no iron overload on MRI T2* value, while 17 (34.0%) had mild iron overload in liver, 5 (10.0%) had moderate and 2 cases had severe iron overload.

Analysing the duration of disease among the cases by age showed that 24 cases among total 34 cases aged less than 17 years (70.6%) had disease for 5 to 9 years and 6 (17.6%) had it for 10 to 14 years, while all 8 cases aged 17 to 26 years had the disease for 15 to 19 years. However, association between age and iron overload severity was found to be statistically not significant (p=0.619). The association of sex and iron overload severity, too, failed to show statistically significant association. While female cases with no iron overload were 9 out of 17(52.9%), the proportion of male cases without any iron overload was 51.5% (16 out of 33 cases) (p=1.000).

Table 2: Interpretation of liver iron concentration based on MRI T2* value.

Liver iron overload	N (%)
Severe overload (<1.4 msec)	2 (4)
Moderate overload (1.4-2.7 msec)	5 (10)
Mild overload (2.8-6.3 msec)	17 (34)
No overload (>6.3 msec)	26 (52)

Association of known condition among the enrolled cases and severity of iron overload based on MRI T2* value (msec) in liver, however, showed statistical significance with 57.5% cases having thalassemia major (23 out of 40 cases) and one case out of 3 MDS cases, having iron overload and rest of the causes (thalassemia minor, sickle cell anaemia and primary haemochromatosis) having no iron overload (p=0.011). Thus, thalassemia major seems to be the main cause associated with iron overload in the present study. The association of duration of disease and iron overload severity, similar to that with age of cases and sex of cases was not found to be statistically significant (p=0.165).

The observations were possible only due to estimation and quantification of liver iron concentration by T2* magnetic resonance imaging as a simple and accessible technique for measurement of liver iron. This further helped identifying cases with iron overload, despite the fact that almost all of these cases were already on chelation therapy.

A higher MRI T2* value indicated absent or lower iron overload. Correlation of MRI T2* value with serum ferritin, age, duration of disease and number of blood transfusions showed it to be statistically are negatively correlated with serum ferritin (r=-0.638; p=0.000) and number of blood transfusions (r=-0.585; p=0.000) lower the MRI T2* value, significantly higher serum ferritin and number of blood transfusions or vice versa.

DISCUSSION

The present study was carried out with an aim to estimate and quantify liver iron concentration by T2* magnetic resonance imaging for measurement of liver iron among all patients who are at high risk of iron overload (e.g., primary hemochromatosis, severe chronic hemolysis of any cause, multiple frequent blood transfusions, either whole blood or red blood cells etc.) who were referred for the same to radiology department of a tertiary level institute over a

period of one year. A total of 50 cases were enrolled for the present study. This could help in early diagnosis, categorisation and prompt treatment or change in treatment modalities among cases with iron overload.

Table 3: Association of the demographic characteristics and interpretation of severity of iron overload among the patients.

Demographic characteristics	Interpretation of severity of iron overload					Total	Chi-square; p value
		Severe	Moderate	Mild	No iron overload		
Age (in years)							
7 to 16	No.	0	1	14	19	34	$\chi2=25.018$; p=0.00295
	%	0.0	2.9	41.2	55.9	100.0	
17 to 26	No.	2	3	2	1	8	
	%	25.0	37.5	25.0	12.5	100.0	
37 to 46	No.	0	1	0	3	4	
	%	0.0	25.0	0.0	75.0	100.0	
47 and more	No.	0	0	1	3	4	
	%	0.0	0.0	25.0	75.0	100.0	
Total	No.	2	5	17	26	50	
	%	4.0	10.0	34.0	52.0	100.0	
Sex							
Female	No.	1	0	7	9	17	$\chi2=3.198$; p=0.362
	%	5.9	0.0	41.2	52.9	100.0	
Male	No.	1	5	10	17	33	
	%	3.0	15.2	30.3	51.5	100.0	
Total	No.	2	5	17	26	50	
	%	4.0	10.0	34.0	52.0	100.0	
Known case							
Thalassemia major	No.	2	5	16	17	40	$\chi2=8.474$; p=0.747
	%	5.0	12.5	40.0	42.5	100.0	
Thalassemia minor	No.	0	0	0	3	3	
	%	0.0	0.0	0.0	100.0	100.0	
Sickle cell anemia	No.	0	0	0	3	3	
	%	0.0	0.0	0.0	100.0	100.0	
MDS	No.	0	0	1	2	3	
	%	0.0	0.0	33.3	66.7	100.0	
Primary haemo-chromatosis	No.	0	0	0	1	1	
	%	0.0	0.0	0.0	100.0	100.0	
Total	No.	2	5	17	26	50	
	%	4.0	10.0	34.0	52.0	100.0	
Duration of disease (in years)							
<5	No.	0	0	2	5	7	$\chi2=3.198$; p=0.362
	%	0.0	0.0	28.6	71.4	100.0	
5 to 9	No.	0	1	9	14	24	
	%	0.0	4.2	37.5	58.3	100.0	
10 to 14	No.	0	0	3	3	6	
	%	0.0	0.0	50.0	50.0	100.0	
15 to 19	No.	2	3	3	1	9	
	%	22.2	33.3	33.3	11.1	100.	
20 and more	No.	0	1	0	3	4	
	%	0.0	25.0	0.0	75.0	100.0	
Total	No.	2	5	17	26	50	
	%	4.0%	10.0%	34.0%	52.0%	100.0	
Compliance							
Yes	No.	0	3	11	26	40	$\chi2=22.986$; p=0.028
	%	0.0	7.5	27.5	65.0	100.0	
No	No.	2	2	6	0	10	
	%	20.0	20.0	60.0	0.0	100.0	
Total	No.	2	5	17	26	50	
	%	4.0	10.0	34.0	52.0	100.0	

Table 4: Correlation among the cases between serum ferritin value and various variables.

Variables		MRI T2*value	Serum ferritin (ng/ml)	Age (in years)	Duration of disease (in years)	No. of blood transfusions
MRI T2*value (msec)	*r*	1	-0.638**	0.231	-0.085	-0.585**
	p value		0.000	0.107	0.559	0.000
Serum ferritin (ng/ml)	*r*	-0.638**	1	-0.038	0.372**	0.800**
	p value	0.000		0.791	0.008	0.000
Age (in years)	*r*	0.231	-0.038	1	0.276	-0.043
	p value	0.107	0.791		0.052	0.771
Duration of disease (in years)	*r*	-0.085	0.372**	0.276	1	0.472**
	p value	0.559	0.008	0.052		0.001
No. of blood transfusions	*r*	-0.585**	0.800**	-0.043	0.472**	1
	p value	0.000	0.000	0.771	0.001	

**Correlation is significant at the 0.01 level (two tailed). Pearson product-moment correlation applied.

In the present study, thirty-four cases (68.0%) were aged 7 to 16 years and 8 (16.0%) aged 17 to 26 years, accounting for 84% of all cases. This predominance was as a result of most cases suffering from thalassemia major (all 34 cases aged 7 to 16 years; 7 cases aged 17 to 26 years), which are invariably young or in their early adulthood by the time the repetitive blood transfusions in this condition starts causing iron overload. In a study by Yang et al, among 201 thalassemia major cases, the age range was 4 to 25 years and 90.5% cases were aged less than 15 years.[11] The present study observed that male cases were slightly higher in proportion (33 cases; 66.0%) as compared to female cases. This proves the known finding that men are significantly more likely to develop hemochromatosis than women and clinically present it earlier than women as women usually have lower iron stores than men mainly due to the physiological loss of blood. Similar proportion was also found by Yang et al, in their study, among TM cases where 62.2% cases were males.[11] Al-Kherbash et al, observed in their study slight male predominance (53.2%) with a male to female ratio of 1.14:1.[12]

A study by Bhukhanvala et al, in Surat city, showed overall prevalence of β-thalassemia trait and sickle cell trait to be 3.2% and 1.38%, respectively.[13] Interpretation of iron overload on MRI T2* was analysed with various demographic, disease related and therapeutic variables to know its association with them. In case of SGOT, while 12 among 26 cases with no iron overload (46.2%) had high SGOT, the percentage increased to 10 out of 17 cases (58.8%) with mild iron overload, further peaking to 100.0% among 5 and 2 cases with moderate and severe iron overload respectively (p-value=0.139, statistically not significant). In case of SGPT, too, 16 cases among 26 with no iron overload (61.5%) had high SGPT, rising to 70.6% among 17 cases with mild iron overload, further reaching a maximum of 100.0% among 5 and 2 cases with moderate and severe iron overload respectively (p-value=0.294, statistically not significant).

In the present study, quantification and categorisation of MRI T2* value in liver was done to assess iron overload, the numeric values of MRI T2*, serum ferritin, age, duration of disease and number of blood transfusions were correlated with each other. Pepe et al, in their correlation study however found that serum ferritin was poorly, yet statistically significantly and negatively correlated with global heart T2* values (r=-0.425; p<0.0001).[14]

Almost similar poor, but statistically significant and negative correlation between serum ferritin levels and T2 hepatic MRI (r=-0.290, p value=0.003) was found by Karimi et al.[15]

CONCLUSION

A cross-sectional observational study was carried out with 50 cases that referred from hematology clinic for MRI scan. No age-wise increase in severity of iron overload was observed. Gender too had no association with iron overload. 66% of male predominance was seen in the study and mean duration of disease among the patients was 10.52±6.06 years, with a range duration of disease was 1 and 26 years. 8% had compliance to visit and treatment among the enrolled cases. Highest abnormality was found in serum ferritin, followed by high level of SGOT and SGPT, 2D echo ejection fraction reduction and high FBS too were found among 38% and 22% cases respectively. T2* imaging technique value obtained in milliseconds were used to determine iron overload and interpretation of liver iron concentration based on MRI. The severity of iron overload on MRI T2* also increased with increasing duration of disease. MRI T2* was considered to be the gold standard for estimation of liver iron overload in patients. Thus, MRI T2* value can be utilized as an investigative technique for diagnosis which could help in early diagnosis, categorization and prompt treatment or change in treatment modalities among cases with iron overload.

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REFERENCES

1. Andrews NC, Schmidt PJ. Iron homeostatis. Ann Rev Physiol. 2007;69:69-85.
2. Batts KP. Iron overload syndromes and the liver. Mod Pathol. 2007;20:S31-9.
3. Brazier Y. Iron overload disorder: All you need to know, 2007. Available at: 2007https://www. medicalnewstoday.com/articles/166455.php.
4. Di Tucci AA, Matta G, Deplano S, Gabbas A, Depau C, Derudas D, et al. Myocardial iron overload assessment by T2* magnetic resonance imaging in adult transfusion dependent patients with acquired anemias. Haematol. 2008 Sep 1;93(9):1385-8.
5. Konen E, Ghoti H, Goitein O, Winder A, Kushnir T, Eshet Y, et al. No evidence for myocardial iron overload in multitransfused patients with myelodysplastic syndrome using cardiac magnetic resonance T2* technique. Am J Hematol. 2007 Nov;82(11):1013-6.
6. Sirlin CB, Reeder SB. Magnetic resonance imaging quantification of liver iron. Magnetic Resonance Imaging Clinics. 2010 Aug 1;18(3):359-81.
7. Hernando D, Levin YS, Sirlin CB, Reeder SB. Quantification of liver iron with MRI: state of the art and remaining challenges. J Magnetic Resonance Imaging. 2014 Nov;40(5):1003-21.
8. Hentze MW, Muckenthaler MU, Andrews NC. Balancing acts: molecular control of mammalian iron metabolism. cell. 2004 Apr 30;117(3):285-97.
9. Brissot P, Troadec MB, Bardou-Jacquet E, Le Lan C, Jouanolle AM, Deugnier Y, et al. Current approach to hemochromatosis. Blood reviews. 2008 Jul 1;22(4):195-210.
10. Fischer R, Harmatz PR. Non-invasive assessment of tissue iron overload. Hematology Am Soc Hematol Educ Program. 2009:215-21.
11. Yang G, Liu R, Peng P, Long L, Zhang X, Yang W, et al. How early can myocardial iron overload occur in beta thalassemia major?. PLoS One. 2014 Jan 22;9(1):e85379.
12. Al-Kherbash HA, Al-Awdi A, Hasan NS. Pattern and clinical profile of thalassemia among pediatric patients attending the Yemeni Society Centers for Thalassemia and Genetic Blood Disorders in Yemen. Sci J Al-Azhar Med Faculty, Girls. 2017 May 1;1(2):43-56.
13. Bhukhanvala DS, Sorathiya SM, Shah AP, Patel AG, Gupte SC. Prevalence and hematological profile of β-thalassemia and sickle cell anemia in four communities of Surat city. Ind J Human Genetics. 2012 May;18(2):167-71.
14. Pepe A, Meloni A, Casale M, Neri MG, Bitti PP, Macchi S, et al. Association between serum ferritin and liver iron concentration with cardiac iron in paediatric thalassemia major patients. Blood. 2015;126(23):956.
15. Karimi M, Amirmoezi F, Haghpanah S, Ostad S, Lotfi M, Sefidbakht S, et al. Correlation of serum ferritin levels with hepatic MRI T2 and liver iron concentration in non-transfusion beta-thalassemia intermediate patients: a contemporary issue. Pediatr Hematol Oncol. 2017;34(5):292-7.

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