Evaluation of the relationship between splenic iron overload and liver, heart and muscle features evident on T2*-weighted magnetic resonance imaging

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Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online)

Adv Clin Exp Med. 2020;29(4):475–480

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Funding sources

None declared

Conflict of interest

None declared

Received on September 22, 2017

Reviewed on April 16, 2018

Accepted on January 21, 2020

Published online on May 5, 2020

Abstract

Background. Splenic iron overload is the most common clinical condition in patients with thalassemia. However, few studies of the effects of splenectomy have been published.

Objectives. To evaluate the relationship between splenic iron overload and liver, heart and muscle features visible in T2*-weighted magnetic resonance imaging, and to investigate the effects of splenectomy on these tissues in patients with beta-thalassemia major (TM).

Material and methods. We retrospectively included 131 patients (76 male and 55 female) diagnosed with TM. All radiological assessments were performed with the aid of a Philips Achieva 1.5T scanner running a multiecho gradient-echo sequence. Hepatic and splenic T2* values were assessed in the same gradient multiecho series. Muscle T2* values were assessed in the shoulder girdle muscles adjacent to the heart area. The relationships among splenic T2*, hepatic T2*, cardiac T2* and muscle T2* parameters, serum ferritin levels, age and other parameters were evaluated.

Results. The splenic T2* value correlated with serum ferritin level and the hepatic T2* value ($p < 0.001$ and $p < 0.001$, respectively). The splenic T2* value did not correlate with age, cardiac or muscle T2* values, or with spleen size ($p = 0.27, 0.21, 0.99$, and 0.39 , respectively). The muscle T2* value correlated weakly with the serum ferritin level ($p = 0.022$). The cardiac T2* value was lower and the liver size greater in patients who had undergone splenectomy compared with those who had not ($p < 0.001$ and 0.001 , respectively).

Conclusions. Splenic iron overload correlated with hepatic overload and the serum ferritin level. Splenectomy increased cardiac iron overload and triggered liver enlargement. However, the muscle iron overload was low and the muscles were therefore unaffected by splenectomy.

Key words: spleen, iron overload, MR imaging, thalassemia

Cite as

Güli Çetinçakmak MG, Hattapoğlu S, Söker M, et al.
Evaluation of the relationship between splenic iron overload and liver, heart and muscle features evident on T2*-weighted magnetic resonance imaging. *Adv Clin Exp Med.* 2020;29(4):475–480. doi:10.17219/acem/116758

DOI

10.17219/acem/116758

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Introduction

Beta-thalassemia major (TM) is a hereditary form of hemolytic anemia characterized by impaired globin B-chain output. Patients with TM require red blood cell transfusions every 2 to 3 weeks. In these patients, senescent native and transfusional erythrocytes are eliminated by the Kupffer cells (phagocytic macrophages) of the spleen and liver, and the released iron is subsequently transported to the plasma by ferroportin.¹ As the total body iron level increases after multiple transfusions and enhanced intestinal absorption, excess iron is stored in the liver and spleen.^{1,2} In thalassemia, the transfusion requirements are increased by spleen hyperactivity, which is often evident in the first decade of life. This condition is termed “hypersplenism” and is treated with splenectomy.³

Assessments of tissue iron overload may be either invasive or noninvasive. Biopsies can be used to assess hepatic iron overload,^{4,5} but are compromised by standardization problems and the risk of complications. Magnetic resonance imaging (MRI) is a noninvasive method frequently used to assess tissue iron overload, and is the only option for assessing iron overload in the heart, since cardiac biopsies are more variable and more dangerous than hepatic biopsies.⁶

Many studies have been conducted on cardiac and hepatic iron overload.^{5,7–10} The spleen is the second most common iron deposition site, after the liver. However, in some studies on splenic iron overload, contradictory results have been reported.^{11–14}

In the present study, we evaluated the relationships among splenic iron overload and that of the liver, heart and muscles, as well as the effects of splenectomy on these tissues in TM patients using T2*-weighted MRI.

Material and methods

Patients

We retrospectively studied 131 TM patients – 76 (58%) men and 55 (42%) women – referred to our clinic between April 2014 and December 2016 for assessments of cardiac and hepatic iron overload using gradient echo (GRE) T2*-weighted MRI. Patients with thalassemia intermedia and primary hemochromatosis were excluded, as were those yielding poor quality MR images. The study was approved by our local ethics committee.

Cardiomuscular and hepatic-splenic examinations

All radiological assessments were performed using an Achieva 1.5-T scanner (Philips, Amsterdam, the Netherlands). Cardiac and hepatic T2*-weighted sequences were obtained using an RC SENSE-body coil (Philips) with electrocardiographic (ECG) respiratory gating. Multiecho gradient echo sequences were obtained from the central liver

Table 1. Splenic, hepatic, cardiac, and muscle multiecho gradient-echo sequences obtained with MRI parameters

MRI parameters	Cardiac and muscle	Liver and spleen
Slace thickness	10 mm	10 mm
FOV	320 × 320	320 × 320
Flip angle	30	45
RT	16 ms	400 ms
Echo times	7 (3, 5, 7, 10, 12, 14 ms)	14 (from 1 to 14 ms with 1 ms increment)

MRI – magnetic resonance imaging; FOV – field of view; RT – repetition time.

zones with transverse plane for the assessment of hepatic T2* values. A short-axis, midventricular, cardiac-gated multiecho gradient echo sequence was used to derive cardiac T2* values (Table 1).

Splenic T2* values were calculated using CMR software (Cardiovascular Imaging Solutions, London, UK). Hepatic and splenic T2* values were calculated using the same echo series. The regions of interest in the spleen and liver covered only tissue. The tissue did not move artifacts outside of vascular and subcapsular spaces. (Fig. 1–2).

The cardiac and muscle T2* values were calculated using the same echo series. Cardiac T2* values were calculated in the mid-ventricular septum (Fig. 3). The muscle T2* values were from shoulder girdle muscles (the subscapular, infrascapular, deltoid, and pectoral muscles) examined in short-axis cardiac sequences (Fig. 4). The calculations were performed using data from regions with no motion artifacts. Within 7 days from the MRI, abdominal ultrasonography (USG) was performed in all the patients; the images were recorded and liver sizes were measured from the midclavicular line of the craniocaudal diameter. Spleen size was taken as the largest diameter on the plane in which the splenic notch was visible. Splenectomy status was recorded. Clinical data including the patients' ages and serum ferritin levels within the previous 2 months was retrieved from their medical records.

Statistical analysis

All the data was evaluated using SPSS v. 18.0 for Windows (SPSS Inc., Chicago, USA). Only the cardiac T2* values and spleen sizes were normally distributed. We used Spearman's rank-order method to seek correlations between the splenic T2* value and age, cardiac and hepatic T2* values, liver and spleen sizes, and serum ferritin levels. The Mann–Whitney U test was used to compare cardiac and hepatic T2* values, liver sizes and serum ferritin levels between patients who had and had not undergone splenectomies.

Results

The 131 patients had a mean age of 12.8 years (range: 4–34 years). There were 39 patients who had undergone splenectomies. The mean splenic T2* value was 9.24

Fig. 1–2. Splenic and hepatic T2* assessments were performed on the central liver zones using a transverse plane multiecho gradient echo sequence. Region of interest (ROI) areas covered only tissue exhibiting no motion artifacts outside of vascular and subcapsular spaces

Fig. 3. Cardiac T2* assessments were performed on the ventricular septum using a short-axis, midventricular, cardiac-gated multiecho gradient echo sequence

(range: 0.75–48.75) in the 92 patients who had not undergone splenectomies. Splenic T2* values correlated moderately with hepatic T2* values ($p < 0.001$, $r = 0.516$) (Fig. 5). Serum ferritin levels correlated strongly with both splenic and hepatic T2* values ($p < 0.001$ and 0.001 ; $r = -0.728$ and -0.707 , respectively). Splenic T2* values correlated weakly with liver size ($p = 0.014$), but not with age, cardiac or muscle T2* values, or spleen size ($p = 0.27, 0.21, 0.99$, and

Table 2. Relationships among splenic T2* values, liver and heart features, and serum ferritin levels

Tissue characteristics and serum ferritin	Median (min–max)	p-value	r-value	n
Splenic size [mm]	122 (68–230)	0.393	–0.9	92
Liver T2* [ms]	2.37 (0.6–28.54)	<0.001	0.516	92
Liver size [mm]	145 (98–206)	0.14	–0.255	92
Cardiac T2* [ms]	27.13 (3.95–51.45)	0.211	0.132	92
Muscle T2* [ms]	28.14 (13.93–38.68)	0.992	0.001	73
Serum ferritin	1,969 (302–19,030)	<0.001	–0.728	55

n – number of patients.

Fig. 5. Scatterplot of the positive correlation between splenic T2* and hepatic T2* values

0.39, respectively) (Table 2). Muscle T2* values correlated with serum ferritin levels ($p = 0.022$, $r = -0.297$) (Table 2).

Cardiac T2* values were lower and liver sizes greater in patients who had undergone splenectomy ($p < 0.001$

Fig. 4. T2* assessments of the left shoulder girdle muscles were done using short-axis cardiac sequences

Table 3. Comparison of iron loads and serum ferritin levels in patients who had and had not undergone splenectomies

Tissue characteristics and serum ferritin	Patients with splenectomy		Patients without splenectomy		p-value
	median	n	median	n	
Liver T2* [ms]	1.86	37	2.42	92	0.421
Liver size [mm]	161	39	141	92	0.001
Cardiac T2* [ms]	22.27	39	29.45	92	<0.001
Muscle T2* [ms]	28.15	30	28.13	73	0.89
Serum ferritin	2,800	18	1,966	37	0.468

n – number of patients.

and 0.001, respectively). However, no significant between-group differences were evident in terms of muscle or hepatic T2* values or serum ferritin level ($p = 0.85$, 0.42 and 0.47 , respectively) (Table 3).

Discussion

Iron is an essential element involved in oxidative processes and is present in hemoglobin, myoglobin and many enzymes. The iron balance is regulated by increasing

or reducing iron absorption. Humans cannot excrete excess iron. In TM patients, the total body iron level increases upon repeated transfusions in association with enhanced intestinal absorption.^{1,15} Moreover, intestinal iron absorption is accelerated by ineffective erythropoiesis and hypoxia. Senescent erythrocytes from transfused blood and cells resulting from ineffective erythropoiesis are digested by the Kupffer cells of the spleen and liver,^{16,17} increasing iron loading and the blood level of non-transferrin bound iron (NTBI). Non-transferrin bound iron triggers iron poisoning. High levels of NTBI often trigger iron accumulation in various organs, particularly the heart, pancreas and pituitary gland. Iron-mediated cardiac toxicity is a major cause of heart failure and death, particularly in TM patients.^{9,18,19} Excess iron in the pituitary gland and other organs triggers major complications including diabetes mellitus and hypogonadism.²⁰

We found strong correlations between splenic T2* and hepatic T2* values and serum ferritin levels, attributable to the presence of Kupffer cells (phagocytosing erythrocytes) in both the liver and spleen. Few prior studies have sought these correlations. Papakonstantinou et al. used T2*-weighted multiecho gradient-echo sequences to compare the signal intensity ratios of the spleen and

liver to that of the right paraspinal muscle. No correlation was apparent, although all signal intensities correlated with the serum ferritin level.¹¹ Brewer et al. found a weak correlation between the extent of splenic and hepatic iron deposition in thalassemia patients.¹² Our present findings differ, perhaps due to the fact that the mean patient ages in both of the studies cited (16.4 and 24.2 years, respectively) were higher than that of our patients (the mean age of patients who had not undergone splenectomy was 11.4 years). Also, the study by Papakonstantinou et al. had a smaller patient series than ours.¹¹

In our study a moderate correlation was apparent between hepatic and cardiac T2* values, but not between splenic and cardiac T2* values. Excessive liver iron overload reduces the accuracy of T2* imaging, attributable to signal constriction and loss. Although the T2* value is a strong indicator of hepatic iron overload, it does not correlate with liver iron concentrations.^{17,21,22} We suggest that the extent of splenic iron overload may be similar to that of the liver.

Splenectomy may have various effects on tissues. We found that although the cardiac T2* value was lower in patients who had undergone splenectomy, no significant between-group differences were evident in terms of muscle T2* values. This indicated that cardiac iron overload increases after a splenectomy, because cardiac energy metabolism is faster than muscle energy metabolism. Moreover, the muscle T2* value correlated only weakly with the serum ferritin level, indicating that iron accumulation by muscles is low. Liver size was increased in patients who had undergone splenectomy, perhaps due to extramedullary hematopoiesis and a response to the iron overload. The spleen and liver are the primary iron deposition tissues in patients with thalassemia and play important roles in protection against increased iron levels.^{11,21} The spleen also eliminates old and defective erythrocytes. However, this function is performed by the liver in patients who have undergone splenectomy. To our knowledge, the study by Brewer et al. is the only work to explore iron overload in patients who have undergone splenectomy. Cardiac iron overload increased in 40 such patients, but the total hepatic iron load did not.¹²

The limitations of our study include the fact that hepatic iron overload was not confirmed by biopsy and we had no control group.

Conclusions

We found that splenic iron overload was strongly correlated with hepatic iron overload and the serum ferritin level. Splenectomy increased cardiac iron overload and liver size in TM patients. However, as the iron overload in muscles was low, this tissue was not affected by splenectomy.

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