Assessment of cardiac and liver iron overload by magnetic resonance imaging in patients with thalassemia major: short-term follow-up

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Abstract
Objective: This study was performed to assess cardiac and hepatic iron overload in young patients with thalassemia.
Methods: We reviewed the medical records of patients with thalassemia at a pediatric hematology clinic who had recently undergone cardiac and hepatic magnetic resonance imaging.
Results: Eleven patients underwent cardiac and hepatic T2* imaging at a mean age of 13.9 ± 4.48 (range, 9–21) years. Three patients had cardiac iron overload and all patients had hepatic iron overload according to the magnetic resonance imaging scan. Ten patients underwent control imaging approximately 1 year later. The mean serum ferritin level at the initial imaging examination was 1820.87 ± 1275.22 (range, 634.04–4221.03) ng/mL. There was a strong negative correlation between the ferritin level and cardiac T2* time and between the blood hemoglobin level and hepatic T2* time. Among the 10 patients who underwent control imaging, the average hemoglobin and ferritin levels significantly decreased from the initial to control imaging examinations, but there was no significant increase in the cardiac and hepatic T2* times.
Conclusions: Cardiac and hepatic T2* imaging is a feasible method of assessing cardiac and hepatic iron overload even before complications and clinical signs of iron overload appear.

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**Introduction**

Patients who receive multiple blood transfusions because of anemia have a risk of secondary hemochromatosis. Patients with thalassemia have a higher risk of iron overload than patients with other hereditary diseases. Cardiac disorders secondary to iron overload are the leading cause of mortality in patients with thalassemia. Cardiac disorders include restrictive and dilative heart failure, myocarditis, pericarditis, and myocardial infarction. Other complications of iron overload in patients with thalassemia are liver failure/cirrhosis and endocrine organ failure.

Measurement of the serum ferritin level is a frequently used method of iron overload assessment, but it does not indicate the actual presence of cardiac iron overload. The T2* time, calculated by the T2* weighted imaging gradient echo magnetic resonance imaging (MRI) sequence, decreases with iron-related magnetic inhomogeneity and is a quantitative value measured in milliseconds.

In this study, we assessed cardiac and hepatic iron overload using MRI in transfusion-dependent patients with thalassemia major.

**Materials and methods**

The Eskisehir Osmangazi University ethics committee approved this retrospective study (Approval number: 25403353-050.99-E.54477). The requirement for informed consent was waived by the ethics committee because of the retrospective nature of the study.

We retrospectively reviewed patients who had been diagnosed with and treated for thalassemia major at our pediatric hematology-oncology clinic and who had undergone cardiac and hepatic MRI scans as well as control MRI scans from January 2017 to March 2018. The medical records of all eligible patients were reviewed. The patients’ demographic data, cardiac and hepatic T2* times, echocardiography findings, blood hemoglobin and ferritin levels, and chelation therapy dose were obtained from the hospital records. The blood hemoglobin and ferritin levels were defined as the average of those obtained during the 2 years before the first MRI scan. If the patient had undergone a control MRI scan, the chelation dose and the mean blood hemoglobin and ferritin levels between the two imaging examinations were recorded.

All cardiac and hepatic T2* images were obtained with a 3T MRI scanner. The cardiac T2* time was obtained from the region of interest at the mid-septum on the short-axis view, and the hepatic T2* time was obtained from the region of interest on the right lobe of the liver in an approximately 1-cm square on the T2* map via the computer software CardiacVX (GE Healthcare, Chicago, IL, USA). The cardiac T2* value was considered severe at $<10$ ms and mild at $\geq 10$ to 20 ms. The hepatic T2* value was considered mild at $>3.8$ to 11.4 ms, moderate at $>1.8$ to 3.8 ms, and severe at $\leq 1.8$ ms.

IBM SPSS version 20.0 (IBM Corp., Armonk, New York, NY, USA) was used for the statistical analysis. Because the values were nonparametric, Spearman’s
rank correlation coefficient was used to assess correlations and the Mann–Whitney U test and Wilcoxon’s test were used to compare the mean values between independent and dependent groups. A P value of <0.05 was considered statistically significant.

Results

We identified 11 patients (5 male, 6 female), who had undergone cardiac and hepatic MRI scans with a 3T MRI scanner, had been diagnosed with thalassemia major, and had undergone regular blood transfusions. Ten of these 11 patients had undergone a second control MRI scan approximately 1 year after the initial imaging examination (mean time between scans, 476 ± 57.5 days; range, 386–563 days).

The mean age of the patients at the time of the first MRI scan was 13.9 ± 4.48 years (range, 9–21 years). No patients had cardiac dysfunction according to the echocardiography results. Six patients underwent a blood transfusion every month, and five patients underwent a blood transfusion every 3 weeks. All but one patient received oral deferasirox chelation therapy, and the mean dose was 1025 ± 362.28 mg/day (range, 750–1500 mg/day) (Table 1).

Three patients had cardiac siderosis (severe in one, mild in two). The ages of these patients were 9, 14, and 15 years, respectively. All patients had hepatic iron overload (mild in four, moderate in five, and severe in two) (Table 2).

The mean serum ferritin level among all 11 patients was 1820.87 ± 1275.22 ng/mL (range, 634.04–4221.03 ng/mL). Patients with and without cardiac siderosis had a mean serum ferritin level of 3373.88 ± 1282.80 ng/mL (range, 1898–4221.03 ng/mL) and 1238.49 ± 657.05 ng/mL (range, 634.04–2262 ng/mL), with a statistically significant difference (P = 0.041). There was a strong, statistically significant negative correlation between the cardiac T2* time and serum ferritin level (r = −0.729, P = 0.011), but there was no statistically significant correlation between the hepatic T2* time and serum ferritin level (r = −0.255).

The mean pretransfusion blood hemoglobin level among all 11 patients was 8.33 ± 0.38 g/dL (range, 7.85–8.90 g/dL). There was no statistically significant difference between patients with and without cardiac siderosis. However, there was a strong negative correlation between the hepatic T2* time and the hemoglobin level (r = −0.601, P = 0.049).

There was no statistically significant difference in the cardiac T2* and hepatic T2*

| Table 2. Distribution of cardiac and hepatic iron overload. |
|----------------------------------------------------------|
| **Hepatic iron overload severity**                        |
| Mild | Moderate | Severe |
| Cardiac siderosis | 1 (9.1) | 1 (9.1) | 1 (9.1) |
| Negative | 3 (27.3) | 4 (36.4) | 1 (9.1) |

Data are presented as n (%).

| Table 1. Patient characteristics. |
|-----------------------------------|
| **Sex, male/female** | 5 (45.4)/6 (54.6) |
| **Age, years** | 13.9 ± 4.48 (9–21) |
| **Chelation** | All patients received oral deferasirox |
| **Chelation dose, mg/day** | 1025 ± 362.28 (750–1500) |
| **Pretransfusion hemoglobin level, g/dL** | 8.33 ± 0.38 (7.85–8.90) |
| **Ferritin level, ng/mL** | 1820.87 ± 1275.22 (634.04–4221.03) |

Data are presented as n (%) or mean ± standard deviation (range).
times between male and female patients at the first and control imaging examinations. The mean hemoglobin and ferritin levels among the 10 patients who underwent control imaging examinations were 8.31 ± 0.41 g/dL (range, 7.85–8.90 g/dL) and 1686.05 ± 1278.56 ng/mL (range, 739.18–4221.03 ng/mL), respectively, before the first imaging examination. Between the first and control imaging examinations, the mean hemoglobin and ferritin levels were 8.12 ± 0.51 g/dL (range, 7.35–8.90 g/dL) and 1260.23 ± 607.16 ng/mL (range, 566.41–2474.77 ng/mL), respectively. Both the ferritin and hemoglobin levels significantly decreased between first and control imaging examinations (P = 0.038 and P = 0.036, respectively). The mean cardiac T2* and hepatic T2* times were 21.07 ± 6.19 ms (range, 8.6–28.0 ms) and 3.62 ± 1.98 ms (range, 1.4–7.6 ms), respectively, at the first imaging examination and 23.01 ± 8.20 ms (range, 7.9–31.0 ms) and 3.72 ± 3.16 ms (range, 1.3–10.0 ms), respectively, at the control imaging examination (Table 3). However, there were no statistically significant increases in the cardiac and hepatic T2* times, and no patient showed improvement in the severity of cardiac or hepatic iron overload.

Discussion

Because of ineffective hematopoiesis, patients with thalassemia develop anemia and increased intestinal absorption of iron. Treatment of thalassemia with blood transfusions is another cause of iron overload. Iron overload leads to oxidative stress and cell membrane impairment. Eventually, the heart, liver, and endocrine glands develop functional impairment, and skeletal changes occur secondary to excessive bone marrow activation.  

Among the various complications of thalassemia, cardiac iron overload and cardiac complications (heart failure and arrhythmia) are the leading mortality factors. Hepatic complications due to iron overload include inflammation, fibrosis, and finally cirrhosis. Measurement of the serum ferritin level is the most commonly used method to monitor iron overload. The ferritin level is very sensitive, but it is not specific because it can increase with inflammation as an acute-phase reactant, in the presence of metabolic disorders, and in the presence of hepatitis. Echocardiography can be used to diagnose cardiac iron overload-related complications only after heart failure begins.

According to the literature, the cardiac and hepatic T2* times are lower in patients with than without thalassemia major, and there is a strong negative correlation between the serum ferritin level and T2* time. The present study showed a strong negative correlation between the serum ferritin level and initial cardiac T2* time, as expected. However, there was no significant correlation between the serum ferritin level and initial hepatic T2* time or between the cardiac and hepatic T2* times. The effect of iron chelation therapy on the liver can increase because of the iron storage function of the liver, and this may explain why

|                | Cardiac T2* time, ms | Hepatic T2* time, ms | Hemoglobin level, g/dL | Ferritin level, ng/mL |
|----------------|----------------------|---------------------|------------------------|-----------------------|
| First MRI      | 21.07                | 3.62                | 8.31                   | 1686.05               |
| Control MRI    | 23.01                | 3.72                | 8.12                   | 1260.23               |

MRI, magnetic resonance imaging.
no significant correlation was found between the cardiac and hepatic T2* times or between the ferritin level and hepatic T2* time.

Our study revealed a negative correlation between the blood hemoglobin level and initial hepatic T2* time, indicating the importance of lower targeted hemoglobin blood levels and fewer blood transfusions to avoid iron overload. A moderate transfusion regimen that targets a subnormal hemoglobin level of 9 to 10 g/dL has been recommended in the literature. Additionally, complications such as hypersplenism or alloimmunization, which require an increased transfusion rate to maintain a subnormal hemoglobin level, must be treated to avoid over-transfusion.

The present study also revealed a statistically significant decrease in the mean ferritin and hemoglobin levels between the first and control imaging examinations of 10 patients. The decrease in the mean hemoglobin level may have been the result of a lower blood transfusion rate, and the decrease in the mean ferritin level may have been the result of both a lower transfusion rate and higher chelation compliance. This suggests that assessment of iron overload may have an influence on both patients and clinicians with respect to chelation compliance and the transfusion regimen. However, there was no statistically significant influence of lower ferritin levels on the cardiac and hepatic T2* times, which can be explained by the small number of patients in our study. Khaled et al. also reported that the serum ferritin level was significantly negatively correlated with the cardiac T2* time but not with the hepatic T2* time in pediatric patients similar to those in our study. Yang et al. described the possibility of cardiac siderosis in pediatric patients with thalassemia as young as 6 years of age in cases of poorly effective chelation therapy. In our study, the youngest patient with cardiac siderosis was 9 years of age, although this patient received effective chelation therapy. Because some patients have no clinical symptoms, assessment and follow-up of iron overload by MRI has a crucial role even in younger patients.

Based on our experience, both cardiac and hepatic T2* MRI is possible in a single session with a single breath-hold because the time needed to acquire the gradient echo T2* sequence is very short. This makes imaging possible without anesthesia even in younger patients.

This study had some limitations. It was retrospective in design, involved a small number of patients, and was performed at a single hospital. Therefore, the results cannot be generalized to all patients with thalassemia. Additionally, no cardiac functional imaging results were available to correlate the cardiac functions with other parameters. Finally, no histopathological assessment of the iron content in the liver and myocardium was performed.

In conclusion, cardiac and hepatic T2* imaging is a feasible method of assessing cardiac and hepatic iron overload even before complications and clinical signs of iron overload appear.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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