Evaluation by MRI of cardiac and hepatic iron overload after hematopoietic stem cell transplantation

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Hematopoietic stem cell transplantation (HSCT) is increasingly used as treatment for a variety of hematopoietic and immunologic disorders. Iron overload, mainly related to transfusion, is a relatively common complication in HSCT recipients. In turn, this overload increases the risk of complications such as infections, veno-occlusive disease or liver dysfunction after transplantation among others (1, 2).

Serum ferritin level determination is widely used as a screening technique to assess the iron status in the body. In this group of patients, the detection of elevated serum ferritin levels is frequent. However, although serum ferritin is a sensitive parameter for iron overload assessment, it is not specific. Ferritin values greater than 1000ng/ml may indicate iron overload, but these values can also be elevated in other conditions such as active inflammatory processes, certain liver diseases or metabolic syndrome (3). It is important to determine whether ferritin increase is due to iron deposition or not to establish the treatment. Iron overload can be treated by phlebotomy or by iron chelating drugs.

The best parameter to evaluate the real iron deposition is the quantification of liver iron concentration (LIC). Liver biopsy is the gold standard but is invasive and not exempt of morbidity. Magnetic resonance imaging (MRI) is a noninvasive technique that has been evaluated in multiple studies for hepatic and cardiac iron overload assessment with very good results (4-9) and is being increasingly used.

The purpose of this study is:

- To determine by MRI the presence of liver and cardiac iron overload in this hematologic group of patients.

- To analyze the correlation of ferritin serum levels with cardiac T2* values and LIC calculated by MRI.
Methods and Materials

Patients

This was a retrospective observational study. 18 patients treated with HSCT because of different haematological disorders (Table 1) were included during 2010 and 2011, seven female and eleven male, aged between 22 and 58 years (mean: 42). All of them were studied by MRI by medical request for iron overload evaluation in the liver and heart. We could not collect the exact number of transfusions received since not all patients were treated exclusively at our centre. In all cases, we collected serum ferritin values (normal value: adult male: # 300ng/ml; adult female: # 200ng/ml).

Magnetic resonance imaging

Liver iron overload was studied by MRI in all cases and in 15 of these, cardiac iron overload was also studied following the model which is explained later (in the other three cases, a different cardiac T2* determination model was followed). MRI scans were performed on a 1.5T MRI (Philips Health Care, Achieva). We evaluated in the same examination LIC by MRI following a model previously validated in our centre (4), left systolic cardiac function by MRI and myocardial T2 *value (T2*M) by means of gradient multiecho T2* sequence. Each study lasted approximately 60 minutes.

Hepatic evaluation

To determine LIC two axial gradient echo sequences were used (proton density and T2: TR/TE/#: 120/4-14/20º), within a single breath hold (mean: 20 seconds). We used the integrated QBody coil.

The signal intensity (SI) in the hepatic parenchyma was measured in three regions of interest (ROI) larger than 1cm² in the right hepatic lobe and in the paravertebral muscles with two ROI placed on the left and on the right paraspinal muscles (Figure 1). The ROI were placed in the same MR section for each sequence. The values obtained were introduced in a spreadsheet to obtain LIC quantification (Figure 2).

Cardiac evaluation

A phase-array coil with five elements was used for the complete cardiac study.
For T2*M measurement, three parallel short axis views (basal, medium and apical) of left ventricle were obtained using multiecho gradient T2* sequence (TR/initial TE/TE interval/ number of echoes/#: 26/1,04/0,8/30/60), with ECG triggering and within approximately 17 seconds breath hold. Each slice was acquired at end diastole.

The signal intensity through echoes was fitted to a monoexponential model described by the equation:

\[ S(TE) = S_0 \exp(-TE/T2*) \]

Where \( S(TE) \) represents the signal intensity for each TE, \( S_0 \) represents the signal at TE equal to zero and \( T2* \) represents the relaxation time. All pixels in the image were analysed to obtain \( T2* \) parametric maps (10). For measurement, ROIs were placed in the \( T2* \) parametric maps in the interventricular septum, in the three slices, excluding endocavitary lumen and avoiding the coronary veins (Figure 3). The mean value of the three measurements was calculated. Patients with a T2*M value greater than 20ms (cardiac iron is not detected) typically do not develop heart dysfunction, whereas patients with T2*M lower than 10ms are at higher risk for cardiac dysfunction (11, 12, 13).

**Statistical analysis**

The description of liver iron overload calculated by MRI was made categorizing LIC according to the following cut-offs:

- CHH # 36µmol / g: absence of hepatic iron overload
- CHH between 37-79µmol / g: moderate overload
- # CHH: 80µmol / g: severe overload

Correlation of T2*M and LIC values with ferritin and between them was obtained by means of Pearson correlation. We used Analysis of Variance to compare mean ferritin levels depending on liver iron overload.
<table>
<thead>
<tr>
<th>Sex</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>11</td>
<td>61,1%</td>
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<tr>
<td>Female</td>
<td>7</td>
<td>38,9%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathology</th>
<th>n</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>ANLL(^{(1)})</td>
<td>5</td>
<td>27,8%</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>3</td>
<td>16,7%</td>
</tr>
<tr>
<td>CML(^{(2)})</td>
<td>2</td>
<td>11,1%</td>
</tr>
<tr>
<td>ANLL after MDS(^{(3)})</td>
<td>2</td>
<td>11,1%</td>
</tr>
<tr>
<td>Biphenotypic AL(^{(4)})</td>
<td>2</td>
<td>11,1%</td>
</tr>
<tr>
<td>MDS</td>
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<td>5,5%</td>
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<tr>
<td>Medullary Aplasia</td>
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<td>5,5%</td>
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<tr>
<td>Limphoblastic AL</td>
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<td>5,5%</td>
</tr>
<tr>
<td>Ritcher syndrome</td>
<td>1</td>
<td>5,5%</td>
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<table>
<thead>
<tr>
<th>Age (years)</th>
<th>n</th>
<th>minimum-maximum</th>
<th>mean</th>
<th>standard deviation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>18</td>
<td>22-58</td>
<td>42,39</td>
<td>10,1</td>
</tr>
</tbody>
</table>

\(^{(1)}\) Acute non lymphoblastic leukemia. \(^{(2)}\)Cronic myeloid leukemia. \(^{(3)}\) Myelodyplastic syndrome. \(^{(4)}\) Acute leukemia.

Table 1

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Fig. 1: ROIs placement on liver parenchyma and paravertebral muscle.

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**Fig. 2:** Spreadsheet. SI liver/SI muscle ratio to quantify LIC.

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**Fig. 3:** ROI placement on the interventricular septum.

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Results

LIC, T2*M and ferritin values are described in table 2.

Serum ferritin was elevated in 17 cases. In twelve of these cases, ferritin was greater than 1000ng/ml.

LIC was normal in five patients (27.8%), in four was indicative of moderated iron overload (22%) and in nine (50%) indicated severe iron overload (Figure 4).

In the 15 cases for which iron overload was also evaluated in the heart, T2*M values obtained were greater than 20ms. No patient had T2*M values suggestive of cardiac iron overload.

All patients with ferritin higher than 1000ng/ml had severe (nine) or moderate (three) hepatic iron overload. Four patients had elevated serum ferritin values without hepatic iron overload, three of which had ferritin values near 1000ng/ml (878.5 to 970.7ng/ml). In one case, ferritin was slightly elevated and LIC was indicative of moderate hepatic iron overload. In one case LIC and ferritin were normal.

The mean ferritin value is lower in the group of patients without liver iron overload than in the group of high and moderated hepatic iron overload. The difference between the mean ferritin value for the group of patients without overloading with respect to those with severe overload is significant (p: 0.01) but the difference is not significant between mean ferritin of these two groups and the mean ferritin of the group with moderate overload, for which ferritin values showed a wide variability (Figure 5).

The correlation between serum ferritin and LIC was good and statistically significant (r = 0.6, p: 0.08. Figure 6).

Correlation between ferritin and T2*M values was weak and not significant (r: -0.27, p: 0.3. Fig. 7).
## TABLE 2: Variables description

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>minimum</th>
<th>maximum</th>
<th>mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin</td>
<td>18</td>
<td>197</td>
<td>3947</td>
<td>1712,1</td>
<td>1054,5</td>
</tr>
<tr>
<td>(ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIC</td>
<td>18</td>
<td>17</td>
<td>281</td>
<td>98,9</td>
<td>79,1</td>
</tr>
<tr>
<td>(μmol/g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2*M</td>
<td>15</td>
<td>24,1</td>
<td>39,3</td>
<td>30,2</td>
<td>4,3</td>
</tr>
<tr>
<td>(ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2

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Fig. 4: Patients distribution according to LIC.

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**Fig. 5:** Serum ferritin mean value and confidence interval related to LIC

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Fig. 6: Serum ferritin and LIC estimated by MRI correlation

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Fig. 7: Serum ferritin and T2*M values correlation.

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Conclusion

In our study, 72.2% of patients with HSCT assessed by MRI showed moderate or high hepatic iron overload. However, cardiac iron overload was not detected.

All patients with serum ferritin higher than 1000ng/ml had moderate or severe iron overload.

23.5% of 17 patients with elevated serum ferritin showed normal LIC values.

MRI may play an important role in determining whether the elevation of serum ferritin is due to actual iron overload or due to other different causes and thereby contribute to the therapeutic strategy.
References


