MRI assessment of changes in liver iron deposition post venesection

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Authors: P. Beddy, J. McCann, M. Ahern, S. Norris, M. T. Keogan; Dublin/IE
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Purpose

The aim of this study was to determine if changes in hepatic iron content in patients with hemochromatosis pre and post venesection could be detected by changes in liver signal intensity with MRI.
Methods and Materials

This was a prospective observational study. Between December 2004 and March 2007, 21 patients were recruited with a genetically confirmed diagnosis of hemochromatosis and an elevated serum ferritin. The patients were scheduled to have an MRI scan before and after venesection in the MR imaging department of our institution. The initial MR imaging was performed prior to the patients commencing venesection treatment. A serum ferritin level was measured within 1 week prior to the MR scan. The study was approved by our institution’s Ethics and Research committee. Full written informed consent was obtained from each patient and control subject.

Ten controls were recruited for comparative purposes. The controls were selected from patients undergoing investigation of biliary disease with a Magnetic Resonance Cholangiopancreatography (MRCP). All controls had a normal serum ferritin levels and no history of iron overload. In addition to the standard MRCP protocol they underwent the same sequences as our patient group (see below).

The imaging was performed on a 1.5T MR system (Symphony; Siemens AG, Erlangen, Germany) using a phased array coil. The imaging was optimized to ensure an even signal profile across the images. Three gradient echo-imaging sequences were performed to evaluate the liver. The first sequence was an in / out of phase T1 (FLASH) [TE of 4.54 (in) / 2.27 (out), TR 167, Flip 70°, slice thickness of 8mm, matrix 256 x 134]. Two T2* (FLASH) weighted sequences were then performed [TE of 5, TR 18, Flip 10°, slice thickness 20mm, image matrix 256 x 128]. The two gradient echo T2* sequences had identical parameters except the second sequence had flow compensation with rephasing (T2*r). Four slices were performed for each gradient echo T2* sequence with individual breathholds for each slice resulting in virtually no respiratory artifact.

Patients were then commenced on a regimen of serial venesections until the serum ferritin had normalized. After 3 months of normal serum ferritin levels, the patients were referred for a repeat MR scan with the same sequences as detailed above.

The signal intensity of the liver tissue was compared against a reference standard which was not affected by iron overload. The standard tissue in this study was the paraspinal muscle. This technique has been previously validated [6,7,8]. Signal intensity (SI) of the liver was measured in the right lobe in three regions of interest larger than 1cm². The SI in the paraspinal muscles were measured in two regions of interest (> 1cm²) in the right and left sacrospinalis muscles. The regions of interest were chosen to avoid artifact and vessels and were on the same slice for each sequence. The average liver-to-muscle (L/
M) SI ratios were then calculated for each sequence. The position of the slice chosen for the measurements was approximately the same for all the patients. An experienced abdominal radiologist performed all measurements.

The relationship between the L/M SI ratio of each sequence and the serum ferritin was assessed with Pearson's correlation coefficient. The difference between the L/M SI before and after venesection was analyzed with a 2 tailed paired students t-test.
Results

Of the 21 patients initially recruited, 1 patient died during the study of an unrelated cause and her data was excluded from all analysis. There were 16 male and 4 female patients with a mean age of 54.5 years. The mean ferritin level at recruitment was 1175.2 ng/mL (SD 693.3ng/mL). The mean ferritin level post treatment was 82.3 ng/mL (SD 28.7 ng/mL). The mean interval between the 2 scans was 2.6 years (SD 0.8 years). [SD=standard deviation]

There was a significant increase in the signal intensity ratios of the liver post venesection on all sequences (table 1). The difference in signal intensity pre and post venesection had a normal distribution. The gradient echo T2* imaging had a 3 fold increase in signal intensity ratio post venesection (figure 1 on page 7 and 2 on page 7). The in-phase images had a 2.2 fold increase in signal intensity ratio and the out of phase imaging had a 1.7 times increase.

There was no significant difference between the control group and the patients post venesection. All pulse sequences had almost identical signal intensity ratios post venesection (table 1). The various pulse sequences showed good correlation between the signal intensity of the liver and the serum ferritin level pre venesection (table 2). In Figures 3 and 4, the L/M SI ratio of T2* and T2*r is plotted against the serum ferritin levels pre venesection. There was no other difference between the two types of gradient sequence (flow compensated and non flow compensated) employed.

Table 1. Comparison between the liver / muscle signal intensity ratio pre and post venesection

<table>
<thead>
<tr>
<th></th>
<th>Ferritin (ng/mL)</th>
<th>In-phase L/M SI ratio</th>
<th>Out-phase L/M SI ratio</th>
<th>T2*r L/M SI ratio</th>
<th>T2* L/M SI ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre venesection (±SD)</td>
<td>1175.1 ±693.3</td>
<td>0.36 ±0.25</td>
<td>0.47 ±0.23</td>
<td>0.08 ±0.07</td>
<td>0.08 ±0.07</td>
</tr>
<tr>
<td>Post venesection (±SD)</td>
<td>82.3 ±28.7</td>
<td>0.76 ±0.15</td>
<td>0.79 ±0.19</td>
<td>0.31 ±0.06</td>
<td>0.32 ±0.07</td>
</tr>
</tbody>
</table>
Table 2. Correlation between serum ferritin and liver / muscle signal intensity ratio pre venesection. Pearson's correlation coefficient.

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Pre venesection</th>
</tr>
</thead>
<tbody>
<tr>
<td>In phase</td>
<td>$r = -0.70$</td>
</tr>
<tr>
<td>Out phase</td>
<td>$r = -0.65$</td>
</tr>
<tr>
<td>T2*r</td>
<td>$r = -0.74$</td>
</tr>
<tr>
<td>T2*</td>
<td>$r = -0.72$</td>
</tr>
</tbody>
</table>
Images for this section:

Fig. 0: 1

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Conclusion

The liver is the site of primary iron deposition and is the principal site of toxicity in iron excess. Liver biopsy is the gold standard for iron quantification. However, MRI can measure the liver iron concentration (LIC) by detecting the effect of iron on nearby hydrogen nuclei [3]. The iron within the liver increases the magnetic field heterogeneities and results in a decreased T2 relaxation time of the liver parenchyma which is proportional to the LIC [4,8,10,11]. Gradient echo MR imaging is the most sensitive to the paramagnetic effects of iron [4]. The liver to muscle signal intensity ratio has been shown to be the most reproducible method of liver iron estimation over a wide range of iron concentrations [10]. MRI is safer and more cost effective than liver biopsy and allows evaluation of the iron load throughout the liver. It can also detect associated complications such as cirrhosis and hepatocellular carcinoma [12,13]. There has however been little work assessing the role of MRI at evaluating the change in liver signal intensity after treatment of iron overload states. In patients with Hemochromatosis, a reduction in the serum iron to baseline drastically reduces the risk of morbidity from the disease, as long as complications have not already occurred.

The results of this study demonstrate that the L/M SI ratios return to normal post venesection on all pulse sequences, paralleling serum ferritin. To our knowledge, this is the first study showing that liver signal intensity completely normalizes post venesection in haemochromatosis patients. The greatest change in SI is seen in the T2* gradient echo imaging. There was good correlation between the serum ferritin levels and the L/M signal intensity ratios on all sequences pre venesection, however the gradient echo T2* sequences performed best.

Most studies to date have used MRI to assess iron levels at diagnosis or initiation of treatment. Our data suggests that MR imaging can provide information about a response to treatment, for example in patients with secondary iron overload where serum ferritin may not reflect liver iron content. A recent study on murine models of juvenile hemochromatosis showed that gradient echo MRI is a useful tool at monitoring the iron concentration post iron chelation treatment [14]. MR quantification of the remaining iron overload may guide further treatment and avert a liver biopsy.

In conclusion, the reduction in normal liver signal intensity in patients with hemochromatosis returns to normal post venesection. Iron assessment with MR imaging may be a useful tool in quantifying treatment responses in patients with iron overload states.
References

Personal Information

Dr Peter Beddy FFRRCSI, FRCR
Radiology Fellow, Addenbrookes Hospital and University of Cambridge, Cambridge, UK. peter.beddy@addenbrookes.nhs.uk

Dr Jeff McCann FFRRCSI, FRCR
Radiology Fellow, Department of Radiology, St James' Hospital and Trinity College, Dublin, Ireland

Mary Ahern B.Rad. DCR(R)
Radiographer, Department of Radiology, St James' Hospital and Trinity College, Dublin, Ireland

Prof Suzanne Norris FRCPI, PhD, MSc
Professor of Hepatology, St James' Hospital and Trinity College, Dublin, Ireland

Dr Mary Keogan FRCR, FACR
Consultant Radiologist, St James' Hospital and Trinity College, Dublin, Ireland