MRI of Diffuse Liver Diseases
Fat, Iron, Fibrosis

Andrew T. Trout, MD
Diffuse liver disease

- Wide spectrum of diseases that diffusely involve liver
- In general result in:
  - Accumulation of fat
  - Accumulation of iron
  - Development of lesions
  - Development of fibrosis
Outline

• Brief review of select diffuse liver diseases
• Focus on fat and iron quantification
• In passing:
  – Fibrosis assessment
    • D. Podberesky – Sat 0835 h
  – Liver lesions
    • A. Towbin
## Brief review – select diffuse liver diseases

<table>
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<tr>
<th>Disorder</th>
<th>Fat</th>
<th>Iron</th>
<th>Fibrosis</th>
<th>Lesions</th>
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<tr>
<td>Fatty liver</td>
<td>X</td>
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<tr>
<td>Hemosiderosis / Hemochromatosis</td>
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<td>X</td>
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<td>Gaucher</td>
<td>X</td>
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<tr>
<td>Wilson disease</td>
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<tr>
<td>Glycogen storage</td>
<td>X</td>
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</table>
Fatty liver

- NAFLD – non-alcoholic fatty liver disease
  - Non-EtOH related hepatic steatosis without hepatocyte injury
- NASH – non-alcoholic steatohepatitis
  - Necroinflammation, fibrosis, \( \rightarrow \) cirrhosis in \textit{subset} of patients with NAFLD
Iron deposition

- Hemosiderosis – abnormal accumulation of iron in tissues
  - Generally reticuloendothelial
  - Transfusion, iron supplementation
- Hemochromatosis – hereditary iron overload
  - Excessive absorption of iron by intestines
  - Liver, pancreas, myocardium

Images courtesy of Rachel Sheridan, MD (CCHMC pathology)
Sphingolipidoses

- Lipid storage diseases
  - Deficiencies in lysosomal enzymes
- Multiple subtypes
- Gaucher is prototypical form
Gaucher disease

- Autosomal recessive
- Hepatomegaly (2 x normal)
  - Due to accumulation of lipids in Gaucher cells
  - Fibrosis, cirrhosis, chronic liver failure
- Splenomegaly (20 x normal)
  - Anemia, sequestration
- Steatosis
- Iron deposition
- Treated with enzyme replacement or transplant
Gaucher disease

• Current recommendation:
  – All patients get volumetric MRI* at diagnosis
  – Once or twice yearly MRI* depending on symptoms and therapy

• At CCHMC
  – Volumes  – Iron
  – Fat  – Elastography

Wilson disease

- Autosomal recessive
- Increased intestinal uptake of copper → deposits in liver
  - No paramagnetic effect
- Cirrhosis
- Rare HCC
Glycogen storage disorders

- Multiple subtypes
- Autosomal recessive
- Accumulation of glycogen in liver, kidney, intestine
Glycogen storage disorders

• Liver
  – Hepatomegaly (90 %)
  – Steatosis
  – Hepatic adenomas / adenomatosis (16 %)
    • Mean age of detection = 15 y
    • 64 % multiple
    • 50 % increase in size or number
    • May transform to HCC
  – Other lesions
    • Focal fat / focal sparing
    • FNH
    • Peliosis
  – Some subtypes → cirrhosis

Fat - definitions

• Fat
  – Focal, multifocal
  – Diffuse

• Hepatic steatosis = excessive accumulation of lipid vacuoles within hepatocytes
  – Graded 0 – 3
    • grade 0: ≤ 5 % of cells (normal)
    • grade 1: 5 – 33% of cells
    • grade 2: 34 – 66% of cells
    • grade 3: ≥ 67 % of cells
Fatty liver – why does it matter?

• NAFLD is # 1 chronic liver disease in U.S.
  – Approx. 10 % of children 2 – 19 yo
    • 6.5 million children
  – 38 % of obese children

• 4 – 5 % → cirrhosis
  – 7 % → HCC over 10 years

Fat – normal

• What is normal?
  ≤ 5 % histologically
  < 5.56 % by MR spectroscopy
Fat – MR assessment

- Signal fat fraction
- Proton density fat fraction (PD fat fraction)
Fat – MR assessment

• Signal fat fraction - *indirect*
  – Fraction of hepatic signal from fat

\[ \eta = \frac{F}{W + F} \]

• Proton density fat fraction – *direct*
  – Fraction of mobile protons in fat
Fat – MR assessment

- Signal fat fraction - *indirect*
  - T1 bias
    - $T_{1_{\text{fat}}} > T_{1_{\text{water}}} \rightarrow$ relative amplification of $T_{1_{\text{fat}}}$
  - T2 bias
    - $R-T_{2_{\text{water}}} < R-T_{2_{\text{fat}}} \rightarrow$ relative amplification of $T_{2_{\text{fat}}}$
  - T2* decay
  - Others
Fat – MR assessment

• Proton density fat fraction – *direct*
  – Carefully crafted sequences to control for bias effects
    • Long TR and small flip angle → reduce T1
    • Multiple echoes → correct for T2*
    • More complex calculations
  – Doesn’t suffer multiple confounders of signal fat fraction
## Fat – MR assessment

<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signal fat fraction</td>
<td>Easy</td>
<td>• Indirect measurement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Confounded</td>
</tr>
<tr>
<td>PD fat fraction</td>
<td>• Direct measurement</td>
<td>More complex</td>
</tr>
<tr>
<td></td>
<td>• Relatively unconfounded</td>
<td></td>
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</tbody>
</table>

• Remember – crude pathologic grading
Fat – MR assessment

• With that in mind….

• Focus on more straightforward signal fat fraction techniques
Fat – signal fat fraction

- Fat suppressed technique
- Chemical shift technique
Fat – signal fat fraction

- **Fat suppressed technique**
- **Chemical shift technique**
Fat – signal fat fraction (FS)

• Fat suppressed (FS) technique
  – Assume all signal loss on FS is due to fat
  – 2 sets of images – w/ and w/o fat sat (NO OTHER CHANGES)
Fat – signal fat fraction (FS)

- Fat suppressed (FS) technique

\[ \eta = \frac{(S_{NFS} - S_{FS})}{S_{NFS}} \]

\[ \eta = \frac{268 - 207}{268} \]

\[ \eta = 0.23 \text{ (23 %)} \]

(16 % by chemical shift in same patient)
Fat – signal fat fraction (FS)

• Fat suppressed (FS) technique
  – Assume all signal loss on FS is due to fat
  – 2 sets of images – w/ and w/o fat sat (NO OTHER CHANGES)

\[ \eta = \frac{(S_{\text{NFS}} - S_{\text{FS}})}{S_{\text{NFS}}} \]

– Limitations
  • Must use chemical fat sat (not SPAIR or STIR)
  • Inhomogeneous fat sat (B0 inhomogeneity)
Fat – signal fat fraction

- Fat suppressed technique
- Chemical shift technique
Fat – signal fat fraction (CS)

- Chemical shift
  - Takes advantage of differing precession freq of fat and water protons

\[ S_{IP} = \text{water} + \text{fat} \]
\[ S_{OP} = \text{water} - \text{fat} \]
Fat – signal fat fraction (CS)

\[ S_{IP} = S_W + S_F \]
\[ S_{OP} = S_W - S_F \]

\[ \eta = \frac{|S_{IP} - S_{OP}|}{2 \times S_{IP}} \]
\[ \eta = \frac{(S_W + S_F) - (S_W - S_F)}{2 \times (S_W + S_F)} \]

\[ \eta = \frac{S_F}{S_W + S_F} \]
\[ \eta = \frac{2 \times S_F}{2 \times (S_W + S_F)} \]
Fat – signal fat fraction (CS)

- Chemical shift
  - Sequential (single echo) opposed and in phase GRE images

<table>
<thead>
<tr>
<th>Phase</th>
<th>1.5 T timing</th>
<th>3.0 T timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opposed</td>
<td>~2.3 msec</td>
<td>~1.15 msec</td>
</tr>
<tr>
<td>In</td>
<td>~4.6 msec</td>
<td>~2.3 msec</td>
</tr>
</tbody>
</table>

- Magnitude only vs. complex
Fat – signal fat fraction (CS)

• Measured with ROIs or signal fat fraction map (pixel based)

\[ \eta = \frac{|S_{\text{IP}} - S_{\text{OP}}|}{2 \times S_{\text{IP}}} \]

\[ \eta = \frac{|70 - 41|}{2 \times 70} \]

\[ \eta = 0.207 \]
Fat – signal fat fraction (CS)

• Can be performed with non-sequential out and in phase images by normalizing to spleen
  – Spleen doesn’t accumulate fat

$$\eta = \frac{|S_{IP} - S_{OP}|}{2 \times S_{IP}}$$

$$\eta = \frac{S_{L, IP} - S_{L, OP}}{2 \times S_{S, IP}}$$

• Assumes T2* of liver and spleen is the same
Fat – signal fat fraction (CS)

• Limitations
  – T2* decay
    • OP must be before IP!
    • Progressive signal loss with increasing TE
  – Magnitude form assumes $S_{\text{water}} > S_{\text{fat}}$
    • Fat > 50 % will be erroneously quantified
    • Not a problem with complex CS
Fat – MR assessment

• If you want proton density fat fraction (PDFF)…
Fat – vendor solutions

**GE**
- IDEAL IQ
- 750w only
- 51% fat
- 55% fat

**Philips**
- mDixon-Quant

**Siemens**
- LiverLab

**HepaFat-Scan®**
- MRI Measurement of Liver Fat Fraction

**HepaFat-Scan® Key Features**
- FDA, CE mark and TGA cleared
- Clinically validated against biopsy measurements of liver fat (59 cases)

**GE, Philips and Siemens**
- mDixon with low flip angle, 6 echoes
- Correct for T1, T2, T2* effects, B0 and B1 inhomogeneity and model the 7 fat peaks

**HepaFat**
- In and opposed phase GRE with low flip angle, 3 echoes
- Correct for T1, T2 and T2* effects

Sources:
Fat – MR spectroscopy

• Spectroscopic measurement (MRS)
  – Most accurate method for quantifying liver fat
  – Quantify area under 6 fat-peaks
    • Two dominant peaks buried under water peak
  – Limitations
    • Single voxel
    • Complex
Liver Iron
Iron deposition – why does it matter?

• Free iron $\rightarrow$ increased oxidative stress $\rightarrow$ cell damage
  – Heart – LV hypertrophy, conduction disturbances, myocarditis / myocardial fibrosis
  – Liver – fibrosis, HCC
  – Endocrine – hypogonadism, growth hormone deficiency, diabetes

• Serum iron and transferrin saturation are poor indicators of iron stores
• Serum ferritin can estimate stores but is acute phase reactant
• Liver iron content (LIC) is strongly correlated with body iron stores

Iron – normal

• What is normal?
  0.8 – 1.2 mg / g dry weight

• Increased risk of hepatic fibrosis, diabetes
  > 7 mg / g dry weight

• Greatly increased risk of cardiac disease and early death
  > 15 mg/ g dry weight

Olivieri NF, Brittenham GM. Blood. 1997 Feb 1;89(3):739-61. PMID: 9028304.
Iron – MR assessment

• Iron is paramagnetic ion
  – Paramagnetic = attracted to external magnetic field and form induced internal magnetic field in direction of the external field

• Causes greater than expected signal loss with increasing TE
  – Rate of signal loss:
    • GRE = T2*
    • SE = T2
Iron – MR assessment

• Qualitatively
  – Liver signal on T2 should be greater than skeletal muscle
    • Decreased w/ iron deposition
    • May also see decreased signal in marrow and spleen
  – Loss of signal in phase*
Iron – MR assessment

• Signal intensity ratio

• Relaxometry
Iron – MR assessment

• Signal intensity ratio

• Relaxometry
Iron – Signal intensity ratio (SIR)

• Developed by Gandon et al.

• 5 breath held GRE images acquired with varying TE and flip angle

http://www.radio.univ-rennes1.fr/
SIR sample case
15 yo, hereditary spherocytosis

T1 FFE: TE = 4.6, TR = 120
PD FFE: TE = 4.6, TR = 120
T2 FFE: TE = 9.2, TR = 120
T2+ FFE: TE = 13.8, TR = 120
T2++ FFE: TE = 23, TR = 120

Case from the archives of the University of Michigan courtesy of Ethan Smith, MD
SIR sample case
15 yo, hereditary spherocytosis

T1 FFE: TE = 4.6, TR = 120

PD FFE: TE = 4.6, TR = 120

T2 FFE: TE = 9.2, TR = 120

T2+ FFE: TE = 13.8, TR = 120

T2++ FFE: TE = 23, TR = 120

LIC > 25,000 mcg / g

Case from the archives of the University of Michigan courtesy of Ethan Smith, MD
Iron – Signal intensity ratio (SIR)

- Limited to $\leq 1.5$ T
- Dynamic range: $215 - 25,000$ mcg / g
- 5 breath holds
- Fails to account for fat effects
Iron – MR assessment

• Signal intensity ratio

• Relaxometry
Iron – relaxometry

- Series of echoes with increasing TE
- $T2$ or $T2^*$ calculated from signal decay
  - Inversely proportional to iron content
- Converted to $R2$ or $R2^*$

\[
R2 = \frac{1000}{T2} \quad R2^* = \frac{100}{T2^*}
\]

- $R2$ or $R2^*$ used to calculate iron content

\[
Fe = 0.254 \times R2^* + 0.202
\]

\[
Fe = \left( 29.75 - \sqrt{900.7 - 2.283 \times R2} \right)^{1.424}
\]
Iron – relaxometry

• First echo – as early as possible
  – Higher field strength, faster decay
Iron – relaxometry (R2*)

• R2* (T2*)
  – Single breath hold
    • Wood method:
      – 17 echoes (0.8 – 4.8 msec)*
        » CCHMC: GE: 8 echoes, Philips: 16 echoes
      • Multiple (8 – 12) slices through liver
  – Monoexponential decay curve
    • $S = S_0 e^{(-TE / T2^*)}$
    • $S_0$ = expected signal at time 0
    
    $Fe = 0.254 \times R2^* + 0.202$
Iron – relaxometry (R2*)

LIC 8,440 mcg / g

Sickle cell, transfusion dependent
Iron – relaxometry (R2*)

LIC 8,440 mcg / g

14 mo later
LIC 3,555 mcg / g

Sickle cell, transfusion dependent
Iron – relaxometry (R2*)

- Fails to account for fat effects
- Breaks down at highest iron concentrations
  - Serai et al. – R2* gives same result as R2 when liver iron content <20 mcg/g

- R2* and SIR are highly correlated
Iron – relaxometry (R2)

• R2 (T2)
  – Free breathing 10 min series of seq

\[
Fe = \left( 29.75 - \sqrt{900.7 - 2.283 \times R2} \right)^{1.424}
\]
Iron – relaxometry (R2)

Sickle cell, transfusion dependent

Average Liver Iron Concentration

<table>
<thead>
<tr>
<th>Average Liver Iron Concentration</th>
<th>35.0 mg/g dry tissue</th>
<th>(NR: 0.17–1.8)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>627 mmol/kg dry tissue</td>
<td>(NR: 3–33)</td>
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Note: The area of this liver image used for the FerriScan analysis excludes large vascular structures and other image artefacts.

Authorised by: Service Centre Manager
Iron – relaxometry (T2)

• R2 (T2)
  – More reproducible
    • Less susceptibility to B0
    • Accounts for fat effects
    • Widest dynamic range

  – Multiple breath holds, 10 min sequence
  – Proprietary to Ferriscan
    • Images acquired → sent to Ferriscan → returned in 2 days
    • Requires phantom in field of view
    • Cost
Iron – vendor solutions

**GE**

StarMap

**Philips**

mDixon-Quant / StarQuant

**Siemens**

LiverLab

GE, Philips and Siemens
- mDixon with 6 echoes used for R2* relaxometry

FerriScan
- R2 relaxometry

Sources:
gehealthcare.com (accessed 6/29/2015)
philipshealthcare.com (accessed 6/29/2015)
healthcare siemens.com (accessed 6/29/2015)
resonancehealth.com (accessed 6/29/2015)
Thank you