The interesting case...

Requisition: 47 year-old woman with elevated LFTs

Our Patient

Normal

GRE T1W out-of-phase image

GRE T1W in-phase image

Images from PACS, BIDMC
The interesting case...

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GRE T1W out-of-phase image

↓ signal intensity of liver compared to skeletal muscle

Normal

GRE T1W in-phase image

↑ signal intensity of liver compared to skeletal muscle

Images from PACS, BIDMC
The interesting case...

Requisition: 47 year-old woman with elevated LFTs

Our Patient

GRE T1W out-of-phase image

↓ signal intensity on bottom image compared to top image

GRE T1W in-phase image

↔ signal intensity on bottom image compared to top image

Images from PACS, BIDMC
Based on the findings, the radiologists noted iron deposition in the liver, spleen, bone marrow, and pancreas.

They further characterized the likely etiology of this iron deposition and its clinical implications.

How?
Objectives

1. Principles of magnetic resonance imaging for medical students

2. Patterns of iron deposition seen on MR imaging
Principles of MRI

- “Hydrogen imaging” → H proton as a magnet

An electric current flowing in a loop will produce a magnetic field perpendicular to the loop

Similarly, a spinning hydrogen atom proton acts like a tiny magnet

Images from Pooley RA1
Any atom with an odd number of protons or neutrons has a net magnetic moment and behaves like a bar magnet.

Hydrogen:
1. Is abundant in biologic tissue
2. Has high sensitivity for its MR signal due to its high resonance frequency
Tissue Magnetization, $M$

- A small excess of protons go into the spin-up alignment, so that the tissue placed under $B_0$ has a small net magnetic field ($M$) aligned with $B_0$.

Adapted from Pooley RA\textsuperscript{1}
Precession

Like a spinning top under a gravitational field, a spinning hydrogen proton under a magnetic field will also wobble, or precess, about its axis.

Frequency of precession (Larmor frequency):

The frequency of that precession is related to an intrinsic property of the proton, the gyromagnetic ratio, and the strength of the applied magnetic field, $B_o$. Images from Pooley RA.
Radiofrequency Pulse

- Magnetic resonance
  - Magnetic resonance is defined as the enhanced absorption of energy that occurs when radiofrequency (RF) energy is applied at the Larmor frequency to nuclei of atoms within an external magnetic field.

- Absorption of RF energy causes the net magnetization of tissue, $M$, to rotate away from alignment with $B_o$ towards the transverse plane:

  ![Diagram](RF Pulse)

Adapted from Pooley RA¹
MR Signal

- M has been rotated into the transverse plane with the application of RF energy, but it continues to precess at its Larmor frequency.

- After the RF pulse perturbs M, the tissue relaxes back to equilibrium. As it does so, it retransmits the energy it gained from the RF pulse in the form of the MR signal. This signal decreases as the tissue relaxes to its equilibrium.
The ‘Skinny on MRI’

- The bar magnet-like features of the proton can be exploited.

- The external magnetic field (1.5T, 3.0T, etc) sets up a condition favorable for energy exchange.

- We can apply energy with a radiofrequency (RF) pulse and record the energy given off from relaxation as a signal intensity.

- Image Contrast → Differences in Tissue Relaxation.
Relaxation from a Perturbed State

- Tissue magnetization \((M)\) relaxes to equilibrium (the state imposed by the external magnetic field)

- This relaxation occurs as two simultaneous mechanisms:
  - \(T_1\) relaxation (spin-lattice relaxation)
  - \(T_2\) relaxation (spin-spin relaxation)

- How quickly a given tissue relaxes by each mechanism is an intrinsic property, i.e. fat relaxes differently than water...
T1 Relaxation

- After a 90° RF pulse, M is completely in the transverse plane and the longitudinal magnetization is zero.

- The longitudinal magnetization then grows back, known as the $T_1$ relaxation.
T1 Relaxation

- The time it takes for a tissue to regain 63% of its final value is T1.

- Each tissue undergoes T1 relaxation at its own rate.
T1 Relaxation and Image Sequences

- **Time to Repetition (TR)**
  - In imaging sequences, RF pulses are repeated, and the time between RF pulses is designated the *time to repetition (TR)*.

- **TR, T1, and Equilibrium**
  - Eventually, an equilibrium longitudinal magnetization is reached between TR and T1 relaxation. At short TRs, tissues with short T1s have increased equilibrium longitudinal magnetization compared to tissues with long T1s.
T1 Weighted Images

- Differences between tissues are accentuated at short TR times.

- Therefore, imaging sequences with relatively short TRs will emphasize T1 contrast. **Hence, these are termed T1-weighted images.**
T1 Relaxation and MR Signal

- MR signal increases with increased longitudinal magnetization

  - Short T1 (fat) $\rightarrow$ $\uparrow$ Long. Magnetization $\rightarrow$ $\uparrow$ Signal

  - Long T1 (spleen) $\rightarrow$ $\downarrow$ Long. Magnetization $\rightarrow$ $\downarrow$ Signal
T2 Relaxation

- During the application of a 90° RF pulse, all the protons precess synchronously (“in phase”)

- Immediately following the RF pulse, the protons begin to desynchronize, or “dephase”

- The main cause of dephasing is spin-spin interactions: the precession frequency of a single proton is related to the magnetic field it sees. When two protons come close to each other, they each are affected by \( B_0 \) **AND** the other proton’s magnetic field
T2 Relaxation

- During the time the two protons are close to each other, one proton precesses at a higher frequency and the other at a slower frequency.

- When the protons move apart, they only see $B_0$ and resume precession at the Larmor frequency.

- But, because they spent some time spinning at different frequencies, they’re no longer synchronized, or in phase.
T2 Relaxation

- As time passes, these interactions cause more and more protons to be out of phase with each other.

- After T2 relaxation, the tissue transverse magnetic field decays as fewer and fewer of the tiny magnets are lined up together.

Image from Pooley RA¹
**T2 Relaxation – A decay process**

- A tissue’s T2 is the time it takes a tissue to decrease its transverse magnetization to 37% of initial value *due to spin-spin interaction*.

- Each tissue undergoes T2 relaxation at its own rate.

Images from Pooley RA¹
T2-weighted Images

- Time to Echo
  - The time between the middle of the RF pulse and when the MR signal is recorded is designated the time to echo (TE)

- Greatest difference in tissues’ T2 values:

- Therefore, imaging sequences that have a relatively long TE are T2-weighted images

Image adapted from Pooley RA¹
T2 Relaxation and MR Signal

- MR signal is maximized when transverse magnetization is completely in phase

- Long T2 (CSF) \(\rightarrow\) ↑ Trans. Magnetization \(\rightarrow\) ↑ Signal

- Short T1 (Liver) \(\rightarrow\) ↓ Trans. Magnetization \(\rightarrow\) ↓ Signal
T2* Relaxation

- Dephasing occurs due to individual protons “seeing” different magnetic fields

- There are other reasons for individual protons to “see” different magnetic fields from each other:
  1. External magnetic field ($B_o$) inhomogeneities
  2. Magnetic susceptibility (to be discussed)
  3. Chemical shift effects (for another day’s discussion)

- $T2^*$ is the time it takes for a tissue’s transverse magnetization to decrease to 37% of its starting value due to all effects = $T2 + additional dephasing effects$
Correcting for T2* with Spin-Echo

- Spin-spin dephasing is a random process having to do with proton-proton interactions.

- The other causes of T2* dephasing are due to differences in local magnetic fields that remain constant over time.

- When a 180 RF pulse is applied halfway between the initial RF pulse and the TE, the dephasing due to fixed inhomogeneities becomes rephasing!
T2* Dephasing

- A pulse sequence = strategy used to create an MR image

- There are other types of pulse sequences, the discussion of which is beyond the scope of this presentation

- It should be noted, though, that Gradient-Recalled Echo (GRE) pulse sequences, often used to decrease imaging time, do not use a refocusing RF pulse and therefore bring out T2*-weighted features
Putting T1, T2, TR, and TE Together

- T1 and T2 relaxation occur simultaneously
- T1 and T2 relaxation properties are specific to tissue type

- T1W images: short TR, short TE (short T1 = bright)
- T2W images: long TR, long TE (long T2 = bright)
Magnetic Susceptibility

- Magnetic susceptibility is the tendency of a substance to attract or repel magnetic lines of force
  - **Diamagnetic** substances weakly repel magnetic lines of force
  - **Paramagnetic** substances attract magnetic lines of force
  - **Superparamagnetic** substances strongly attract magnetic lines of force
  - **Ferromagnetic** substances remain permanently magnetized after being removed from a magnetic field
Variations in magnetic susceptibility create magnetic field inhomogeneities, which in turn produce dephasing and MR signal loss.

This signal loss is most pronounced on images with T2*-weighting.

Gradient-recalled echo images are more sensitive to magnetic susceptibility than spin-echo images.
Magnetic Susceptibility and Iron

- **Iron in tissue** creates strong local magnetic field inhomogeneities that ↓ MR signal

- In each of the ensuing cases, we will look at the **difference in signal intensity** in iron-laden tissues between two images created with gradient-recalled echo (GRE) technique: T1-W IN-PHASE (IP) and OUT-OF-PHASE (OP) images.

- The IP-OP sequence has 2 echo times – the longer the TE, the greater time allowed for dephasing, hence signal loss.

- Deposition of iron => loss of signal in tissue on IP (longer echo) images compared to OP images.
Magnetic Susceptibility and Iron

The characteristic findings of tissue iron deposition described in the literature:

1. Decreased signal intensity on T2WI and T2*WI’s

2. For normal liver, signal intensity should be > skeletal muscle on ALL sequences

3. If iron deposition is great enough, decreased signal intensity on T1WI’s
Patterns of Iron Deposition

- **Reticuloendothelial**
  - Transfusion or extravascular hemolysis

- **Parenchymal**
  - Primary and secondary hemochromatosis
  - Intravascular hemolysis

- **Cirrhosis**
  - Siderotic nodules
Iron Metabolism

Dietary iron

Duodenum (average, 1–2 mg per day)

Plasma transferrin (3 mg)

Muscle (myoglobin) (300 mg)

Liver parenchyma (1000 mg)

Bone marrow (300 mg)

Circulating erythrocytes (hemoglobin) (1800 mg)

Reticulo-endothelial macrophages (600 mg)

Storage iron

Utilization

Iron loss

Sloughed mucosal cells
Desquamation
Menstruation
Other blood loss (average, 1–2 mg per day)
Reticuloendothelial Iron Deposition

- Reticuloendothelial macrophages in spleen and bone marrow and Kupffer cells of liver scavenge iron from senescent RBCs.

- The body has no effective mechanism for losing excess iron.

- With repeated transfusions or rhabdomyolysis, iron deposits in the spleen, liver, and bone marrow.

- Iron deposition limited to the RE system has little clinical significance.
Reticuloendothelial Iron Deposition

GRE T1W out-of-phase images

GRE T1W in-phase images

28 yo M with Hodgkin’s Dz s/p multiple chemotherapy regimens and BM transplants

Images from PACS, BIDMC
Reticuloendothelial Iron Deposition

28 yo M with Hodgkin’s Dz s/p multiple chemotherapy regimens and BM transplants

GRE T1W out-of-phase images

↓ signal intensity in liver, spleen, and bone marrow on IP images compared to OP images

GRE T1W in-phase images

Images from PACS, BIDMC
When the storage capacity of the RE system is reached, redistribution of iron to organ parenchyma (cardiac, hepatic, endocrine tissues) is seen.

- RE capacity estimated at 10 g iron (~40 units of PRBCs)

Organ dysfunction and fibrosis as seen with hemochromatosis can then be seen (to be discussed).

Treatment is phlebotomy (often not clinically tolerated in these patients) or chelation therapy.
RE Iron Deposition w/ Parenchymal Redistribution

GRE T1W out-of-phase images

GRE T1W in-phase images

47 yo F with h/o aplastic anemia s/p transfusion > 75 units PRBCs in 3 years

Images from PACS, BIDMC
RE Iron Deposition w/Parenchymal Redistribution

GRE T1W out-of-phase images

GRE T1W in-phase images

47 yo F with h/o aplastic anemia s/p transfusion > 75 units PRBCs in 3 years

↓ signal intensity in liver, spleen, bone marrow, and pancreas on IP images compared to OP images

Images from PACS, BIDMC
Parenchymal Iron Deposition

- Hemochromatosis
- Intravascular hemolysis
Primary Hemochromatosis

- Autosomal recessive disease wherein 2-3x normal amount of iron is absorbed from GI tract

- Iron deposition in liver first, then heart and endocrine organs:
  - Cirrhosis and hepatocellular carcinoma
  - Cardiomyopathy
  - DM, hypopituitarism, hypogonadism, hypoparathyroidism
  - Can also see destructive arthritis

- Most patients asymptomatic until adulthood
Primary Hemochromatosis

- **Diagnosis**
  - Biochemical evidence of iron overload (serum, liver bx)
  - Genetic testing

- **Quantification**
  - Liver biopsy remains gold standard

- **Treatment**
  - Phlebotomy or chelate tx once serum ferritin levels reach a designated threshold
  - If treated before organ damage, life expectancy is normal. Endocrine abnormalities and cirrhosis DO NOT resolve.
Parenchymal Iron Deposition
Primary Hemochromatosis

41 yo F with incidentally noted elevated serum ferritin and transferrin saturation. Subsequent genetic testing proved positive for C282Y homozygosity.

Images from PACS, BIDMC
Parenchymal Iron Deposition
Primary Hemochromatosis

41 yo F with incidentally noted elevated serum ferritin and transferrin saturation. Subsequent genetic testing proved positive for C282Y homozygosity.

GRE T1W out-of-phase image

↓ signal intensity in liver on IP images compared to OP images

GRE T1W in-phase image

↔ or ↑ signal intensity in bone marrow, pancreas, and spleen on IP images compared to OP images

Images from PACS, BIDMC
Primary Hemochromatosis

- This patient’s disease has been caught early: there is only evidence of iron deposition in the liver.

- This has prognostic significance!
Precirrhotic vs. Cirrhotic Primary Hemochromatosis

(Siegelman et al.)

- Almost ALL pts with PH and cirrhosis had decreased signal intensity in the pancreas (10/11)

- ALL pts with PH and without cirrhosis had normal signal intensity in the pancreas (4/4)

- In ALL pts with cirrhosis not secondary to PH, signal intensity in the pancreas was normal (4/4)
Secondary Hemochromatosis

- **Seen in diseases with ineffective erythropoiesis**
  - Thalassemia major, sideroblastic anemia, megaloblastic anemia

- **Spleen and/or bone marrow** may or may not be involved in secondary hemochromatosis (muddies the waters of characterizing parenchymal vs. reticuloendothelial iron deposition)
Intravascular Hemolysis

- Free hemoglobin binds to haptoglobin and is taken up by hepatocytes

- When haptoglobin is saturated, free hemoglobin is filtered by glomerulus and reabsorbed into proximal convoluted tubule cells

- MR: iron deposition in liver +/- kidneys

- No known clinical significance of deposition
Cirrhosis

- Common chronic end-stage liver disease for variety of hepatic insults

- Diffuse architectural disorganization with fibrosis and formation of regenerative nodules
  - MR: preferential atrophy of R lobe with hypertrophy of caudate and lateral segments of L lobe, nodular texture, low signal-intensity nodule, sequelae of portal HTN
Cirrhotic Iron Deposition

- Diffuse hepatocyte iron deposition may be seen
  - Mild elevation, seen in up to 50% of cirrhotic livers

- Siderotic regenerating nodules
  - ~25% of regenerative nodules accumulate iron > surrounding parenchyma
  - Somewhat specific for cirrhosis

- Gamma-Gandy bodies (siderotic nodules) in spleen
  - Present in up to 12% of cirrhotics
  - Provides indirect evidence of portal HTN
Cirrhotic Iron Deposition

51 yo M with h/o alcoholic cirrhosis

Images from PACS, BIDMC
Cirrhotic Iron Deposition

51 yo M with h/o alcoholic cirrhosis

↓ signal intensity in liver on IP images compared to OP images

↓ signal intensity in regenerative nodules compared to surrounding parenchyma

Gamma-Gandy body in spleen

Images from PACS, BIDMC
Future Utility for MRI in Iron Deposition

- MRI may be useful for more than just characterizing the pattern of iron deposition

- Much research currently focuses on using MRI to quantify the degree of iron deposition
MR Quantification of Hepatic Iron Stores? (Gandon Y et al)⁹

- Serum ferritin stores have poor specificity for body iron stores
- Liver biopsy is often used to establish and quantify biochemical evidence of iron overload
MR Quantification of Hepatic Iron Stores? (Gandon Y et al)⁹

- Algorithm based on ratio of signal intensities of liver to skeletal muscle on GRE sequences obtained with 1.5T magnet

- 89% sensitive in detecting clinically relevant hepatic iron (> 60 µmol/g, normal is < 36 µmol/g) with good correlation with tissue quantification from liver bx

- Advantages
  - Noninvasive, eliminates risk of bx w/inadequate tissue, may provide better estimate than biopsy of cirrhotic, heterogeneous liver, less expensive than bx
Conclusions

- Principles of MRI
  - Hydrogen imaging
  - T1 Relaxation
  - T2 and T2* Relaxation

- MR Characterization of Patterns of Iron Deposition
  - Reticuloendothelial
  - Parenchymal
  - Cirrhotic

- MR Quantification of Iron Deposition
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Sources


