Haematology Cases

GP Symposium 2022

James Liang
Consultant Haematologist

Hyperferritinaemia

Case 1

- 56 year old man referred for ferritin 900ug/L
  - NZ European. Father requires regular venesection
  - Increased central obesity
    - BMI 29.1
  - Increased EtOH intake due to lockdown
- PMHX
  - Nil significant
- Medication/Supplements
  - Nil regular
  - Not on vitamin C nor iron supplementation
- Review of system
  - Nil red flags
- Examination
  - Unremarkable
  - No evidence of autoimmune disease

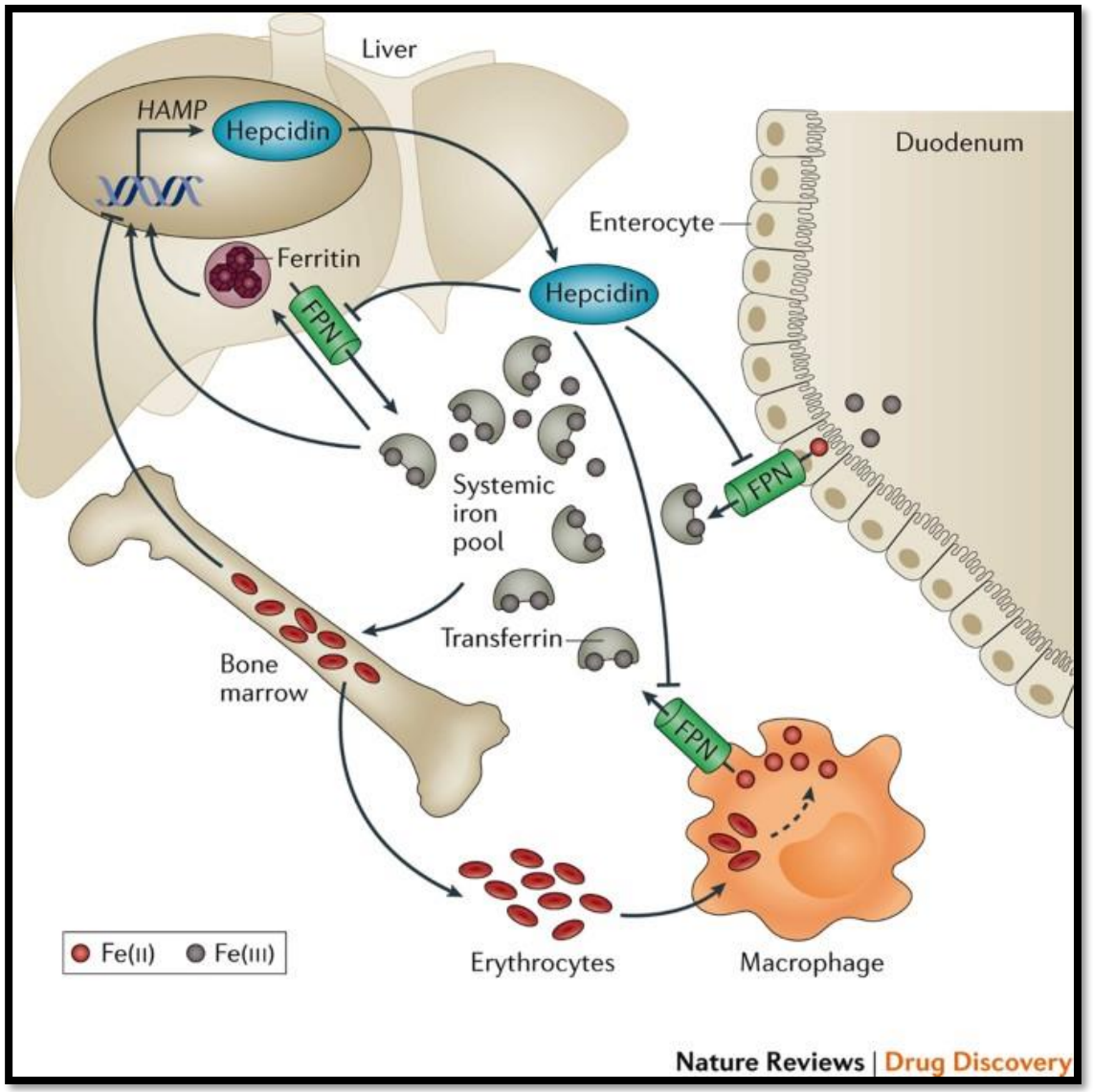
Blood Tests

	26/3/12	12/06/18	18/09/20	05/02/21	
Iron	9	15	15	16	(10-30)
Transferrin	2.4	2.4	2.5	2.5	(1.7-3.4)
Transferrin Sat	0.15	0.25	0.24	0.26	(0.15-0.50)
Ferritin	306	777	900	1329	(20-450)
		5/6/18			
Bilirubin	5	6	7	5	<25
ALP	87	63	82	71	(40-120)
GGT	19	33	36	35	<50
ALT	40	52	60	48	<45

- Molecular Study
  - Negative C282Y (27/4/4 and 29/6/18)
- Other bloods:
  - Normal HbA1c
  - Normal TFT
  - Normal CBC parameter

Differentials

1. True iron overload
   - Increase intake
     - Excessive supplementation
   - Increase absorption
     - HFE gene mutation
     - Vitamin C
     - Other***
2. Liver related
3. Acute phase reactant
   - Infection
   - Inflammation (autoimmune disease/malignancy)
4. Endocrine
   - Hyperthyroidism



Crielaard B et al. Nature Review Drug Discovery 16, 400-423 (2017)

Blood Tests

	26/3/12	12/06/18	18/09/20	05/02/21	
Iron	9	15	15	16	(10-30)
Transferrin	2.4	2.4	2.5	2.5	(1.7-3.4)
Transferrin Sat	0.15	0.25	0.24	0.26	(0.15-0.50)
Ferritin	306	777	900	1329	(20-450)
		5/6/18			
Bilirubin	5	6	7	5	<25
ALP	87	63	82	71	(40-120)
GGT	19	33	36	35	<60
ALT	40	52	60	48	<45

- Molecular Study
  - Negative C282Y (27/4/4 and 29/6/18)
- Other bloods:
  - Normal HbA1c
  - Normal TFT
  - Normal CBC parameter

So what is next?

Iron Overload

- Molecular Study
  - H63D
  - S65C

Other

- Liver
  - USS liver
- Inflammatory/Infection
  - CRP

Results

Iron Overload

- Molecular Study (5/2/21)
  - H63D heterozygous
  - S65C normal

  - Start venesection

Other

- Liver
  - USS liver (25/2/21)
    - Hepatic steatosis
    - Dilated portal vein may suggest early portal hypertension

  - Refer to gastro
    - ShearWave (18/11/21)
      - Mean = 4.8kPa
      - F0/F1 – minimal fibrosis

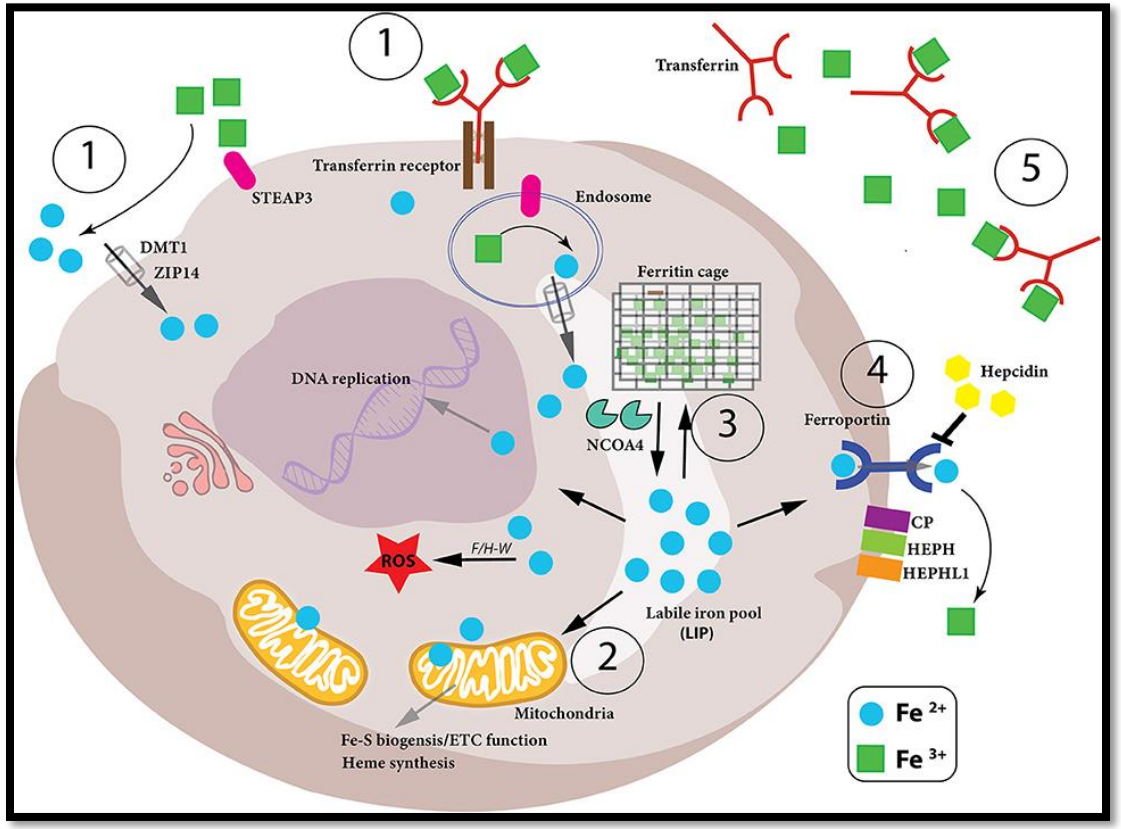
- Inflammatory/Infection
  - CRP normal

HFE gene mutation

HFE gene	Prevalence		Note
	Caucasian	Asian	
C282Y	10-15%	~0%	
H63D	15-40%	4-8%	Mild*
S65C	1-2%	1%	Mild

- Heterozygous HFE mutation normally peak ~600-800ug/L
  - Below 1000ug/L (threshold when end organ damage occurs)

- Compound heterozygous with C282Y can potentially lead to significant iron overload but less likely compared to homozygous C282Y



Cronin et al. Fron. Mol. Biosci, 22 Nov 2019

Case 2

- 43 year old man referred for ferritin 1329ug/L
  - Han Chinese
    - Cousin has high ferritin of unknown cause
  - Since 2017 has lost 10kg currently slightly overweight
    - BMI 24.6
  - No EtOH
- PMHX
  - Previous USS in China (no fatty liver)
- Medication/Supplements
  - Nil regular
  - Not on vitamin C nor iron supplementation
- Review of system
  - Nil red flags
- Examination
  - Unremarkable
  - No evidence of autoimmune disease

Blood Tests

	05/02/21	12/05/21	09/08/21	10/01/22	
Iron	24	23	17	16	(10-30)
Transferrin	2.1	2.1	2.0	2.0	(1.7-3.4)
Transferrin Sat	0.46	0.44	0.34	0.32	(0.15-0.50)
Ferritin	1329	1494	1112	1212	(20-450)
Bilirubin	10		8	4	<25
ALP	42		42	42	(40-120)
GGT	16		16	22	<60
ALT	15		11	19	<45

- Molecular Study
  - Not available
- Other bloods:
  - Normal HbA1c
  - Normal TFT
  - Normal CBC parameter
  - Normal fast lipids

Additional Test

Iron Overload

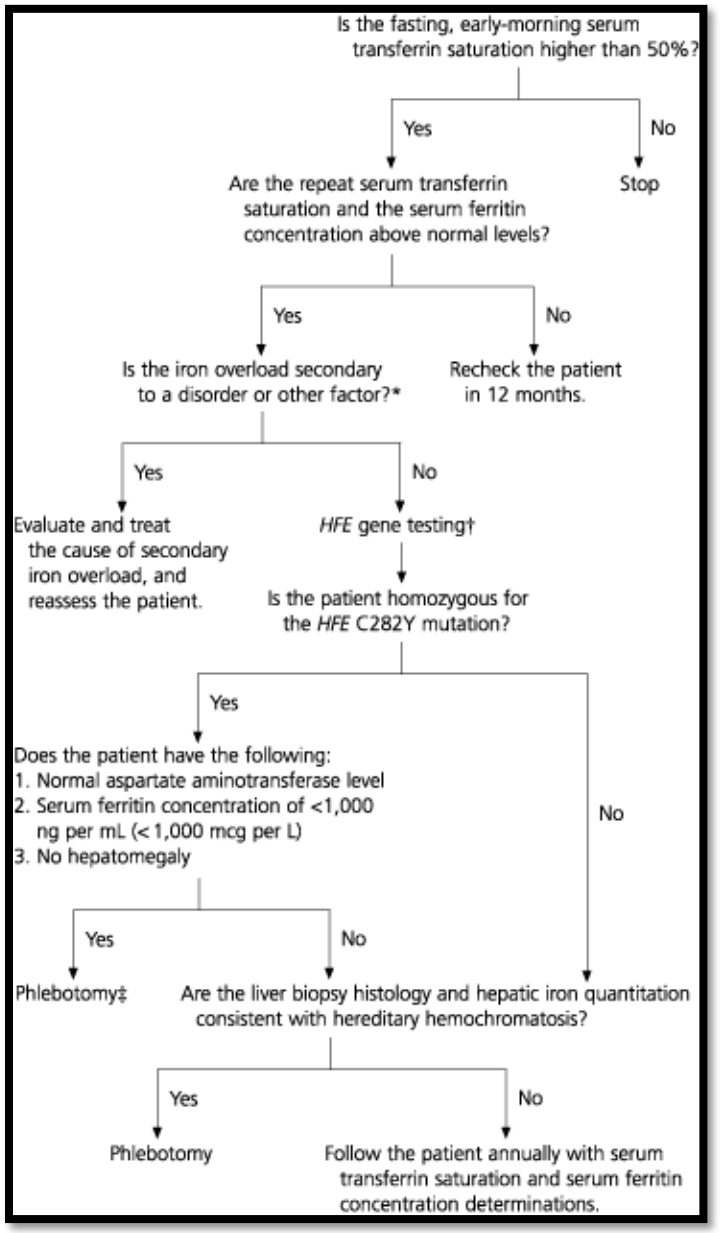
- Molecular Study (16/08/21)
  - C2827 normal
  - H63D normal
  - S65C normal

Other

- Liver
  - USS liver (29/9/21)
    - Normal
- Inflammatory/Infection
  - CRP/ESR normal
  - ANA negative

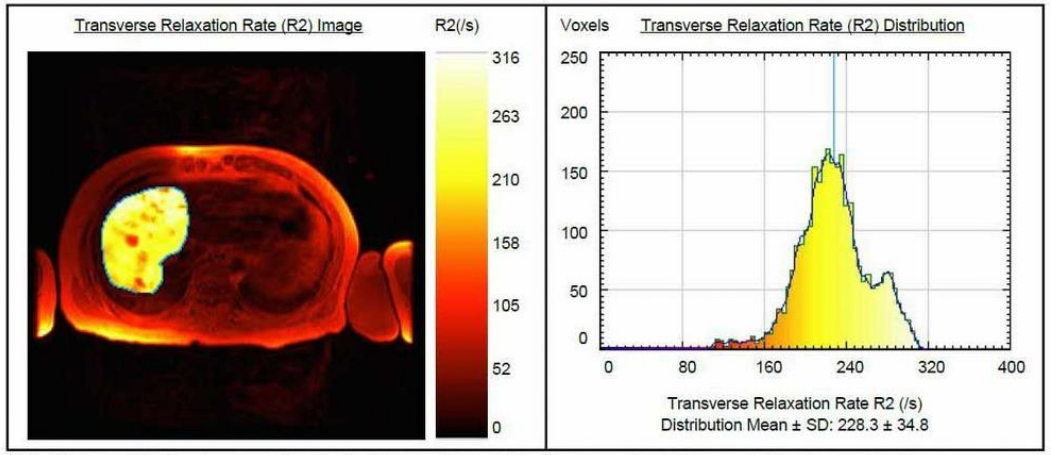
What next?!

- Ultimately
  - Is this due to true iron overload?
  - Is this coming from liver?
- Important to distinguish since treatment is different
- How to do it?
  - Liver biopsy (gold standard)
  - Ferriscan (MRI)
    - Average liver iron
    - More sensitive in identify liver fat



American Academy of Family Physician

Ferriscan



Note: The area of the liver image used for the FerriScan analysis excludes large vascular structures and other image artefacts.

- Ferriscan (24/01/22)
  - Diffuse signal abnormality of the liver in keeping with iron overload.
  - Iron approximately 6mg Fe/g dry weight (0.17-1.8)
  - Fat signal fraction of 28.1%!
    - Normal 5-6%
- Two issues
  - Venesection (true iron overload)
  - On going lifestyle modification
    - Focus on visceral fat

Case 3

- 65 year old woman referred for ferritin >2300ug/L and arthralgia
  - No family history (Chinese)
    - Known to have ferritin >1000 since 2010
    - Iron deficiency 2007
  - Weight stable
    - BMI 26.1
  - No EtOH
  - Use iron wok
- PMHX
  - HTN
  - Dyslipidaemia
- Medication/Supplements
  - Losartan
  - Amlodipine
  - Usana products
- Review of system
  - Under rheumatology but no obvious evidence of autoimmune joint disease
- Examination
  - Changes seen on PIPs and DIPS bilaterally
    - Warm to touch

Blood Tests

	22/01/10	05/04/12	18/06/19	12/02/22	
Iron		24	29	24	(10-30)
Transferrin		2.6	2.8	2.7	(1.7-3.4)
Transferrin Sat		0.37	0.41	0.35	(0.15-0.50)
Ferritin	333	1047	1620	2333	(20-450)
Bilirubin	9		11	7	<25
ALP	60		63	72	(40-120)
GGT	78		50	41	<50
ALT	30		42	36	<45

- Molecular Study
  - Negative C282Y, H63D and S65C
- Other bloods:
  - Normal HbA1c
  - Normal TFT
  - Normal CBC parameter
  - Cholesterol 6.0, HDL 1.96, tri 1.1, LDL 3.5 (ratio 3.1)
  - ESR/CRP normal
  - ANA 1:80
- USS (Feb 2021)
  - Liver mildly hypoechoic consistent with fatty liver disease

Fatty liver?

More results

	20/04/21	10/5/21	12/06/21	27/7/21	2/10/21	6/11/21	14/1/22	
Iron	24	25	20	20	23	28	15	(10-30)
Transferrin	2.9	2.9	2.6	2.9	2.7	2.7	2.6	(1.7-3.4)
Transferrin Sat	0.33	0.34	0.31	0.28	0.41	0.41	0.23	(0.15-0.50)
Ferritin	2050	1905	1767	2016	2577	2577	2748	(20-450)
Bilirubin	7		8	8	7	9	5	<25
ALP	71		78	82	83	85	78	(40-120)
GGT	46		42	39	48	55	44	<50
ALT	29		21	21	21	26	24	<45

Liver Biopsy

- Liver needle biopsy
  - Finding are those of mild simple steatosis with minimal hepatitis activity, mild fibrosis and mild iron deposition, insufficient to confirm haemochromatosis.
    - Fatty liver disease

- Liver iron

• Liver iron concentration	1158 ug/g dry weight	(300-1400)
• Liver iron index	0.3	(0-2)

Take home message

Differential

1. True iron overload
   - Increase intake
     - Excessive supplementation
   - Increase absorption
     - HFE gene mutation
     - Vitamin C
     - Other***
2. Liver related
3. Acute phase reactant
   - Infection
   - Inflammation (autoimmune disease/malignancy)
4. Endocrine
   - Hyperthyroidism

Use Investigations

- Remember the minor HFE genes
  - Pretty useless for non-Caucasians (still has to do them)
- Imaging
  - USS
  - Fibroscan/ShearWave Elastography
  - Ferriscan
- Fatty liver is now the commonest cause of persistent hyperferritinaemia
  - The degree of hyperferritinaemia may not necessary correlate to degree of liver injury
  - LFT may not be helpful either