Clinico-pathological assessment of common medical liver diseases -

Fatty Liver Disease

Judy Wyatt
And
Mervyn Davies
Fat and the liver

- Hepatocytes use lipid (membranes, bile, energy metabolism) but do not normally store it.
- In fatty liver disease, stored triglyceride = steatosis
- A small amount of fatty change is very common - not considered pathological if <5% hepatocytes

- Fatty liver disease = includes steatosis and steatohepatitis and cirrhosis
- Alcoholic liver disease (ALD) or non-alcoholic fatty liver disease (NAFLD)

- Steatohepatitis = metabolic injury, leading to fibrosis and cirrhosis
  - Alcoholic steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH)
### Clinico-Pathological Diagnosis

**Biopsies with fatty change**

<table>
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<th>Steatosis</th>
<th>Steatohepatitis</th>
<th>Fibrosis/stage</th>
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<tr>
<td><strong>alcoholic</strong></td>
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<tr>
<td><strong>Non-alcoholic</strong></td>
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Fatty liver disease is very common – who should have a biopsy?

Estimated prevalence around 30% in Europe

Clinical diagnosis based on:
- Abnormal liver enzymes – can be normal
- Fatty liver on ultrasound
- Aetiology from clinical history – drugs/alcohol and BMI

Why would you do a biopsy??
- Exclude an additional / alternative diagnosis – high ALT, SMA +ve, Medication such as methotrexate
- Stage disease?

Non invasive assessments and NICE guidance?
Fibroscan and other non-invasive measures of fibrosis

In cases where the only question is the extent of fibrosis, then a fibroscan has the potential to replace a liver biopsy – e.g. HCV
Fibroscan

- Non-invasive liver stiffness measurement
- Measures velocity of a low frequency shear wave
- Velocity is directly related to liver stiffness
- Measures a volume of liver 1x4cm at 2.5-6.5cm below skin
- LSM ranges from 2.5-75kPa
Fibroscan and biopsy evaluation of fibrosis
Fibroscan ROC curves
## BARD score

<table>
<thead>
<tr>
<th>Points</th>
<th>1 or 2</th>
<th>ZERO</th>
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<tbody>
<tr>
<td>DIABETES</td>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>BMI &gt;28</td>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>AST/ALT ratio &gt;0.8</td>
<td>Yes = 2</td>
<td>No = 0</td>
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**TOTAL**

A score ≥2 potential for fibrosis. Positive and negative predictive values of the BARD score for advanced fibrosis were 69% and 96%.
NAFLD score

- Age
- Platelets
- Albumin
- Diabetes/impaired glucose tolerance
- ALT
- AST

On line calculator – low risk/intermediate/high

High score (>0.676) positive predictive value for advanced fibrosis (F3-F4) of 82% and a low score (<-1.455) negative predictive value of 88%
ELF Score    European liver fibrosis panel

- Proprietary algorithm
Age
Hyaluronic acid level
PIIIP
TIMP-1
Threshold score of 0.102 sensitivity of 87 to 90% and specificity of 41 to 51% for moderate or severe fibrosis
Threshold >0.457 specificity 95%.
Scores continued

- Fatty liver disease index
  Height
  Weight
  Waist
  GGT
  Triglycerides
The spectrum of fatty liver disease

Case 1. NAFLD, diagnosis, severity, additional diagnosis
Leeds Case 1: Ms JA – born 1963

- 7/16 – referred to abnormal LFT clinic
Age 53, ALT x 1.5, ALP x 1.8
Non Invasive Liver Screen – NILS sent
- Obstructive sleep apnoea
- Morbid obesity – BMI 46
- Diabetes mellitus – metformin and insulin, statin, aspirin, lansoprazole
No alcohol excess (15 units per week) - ?more
Examination palmar erythema
Ms JA born 1963 continued

- BARD score 2, AST/ALT 0.7, NAFLD score indeterminate 0.6, Fibroscan 10.2 (F2 – F3), poor quality markers. ELF not back.

Advised to consider bariatric surgery

Plan biopsy

- *Purpose of the biopsy is to confirm extent of fibrosis, and to examine for presence of steatohepatitis – to inform decision re surgery*
Case 1 Female 53 years. 364697

Morbid obesity, contemplating surgery. Fibroscan gave poor quality markers, so accuracy uncertain. Presumed fatty liver, to determine presence of steatohepatitis and severity of fibrosis.

Additional information from CPC meeting - BMI 46, weighs 140kg, Fibroscan 10.5.
case 1
The NPV & PPV of FS to predict "at least bridging fibrosis" on LB, in patients with NAFLD
case 1

Van Gieson
case 1
case 1
case 1

keratin 8/18
case 1
case 1

Keratin 7
Ms JA continued post bx

- NILS – AMA 1/5,000, IgM normal, IgA 4.4

- Rx UDCA

- Advise referral to bariatric services, since weight loss has previously failed
Steatosis - terminology

- Macrovesicular steatosis – one large droplet displacing nucleus or several small droplets

- Purely microvesicular steatosis – rare, severe, urgent – e.g. acute fatty liver of pregnancy, Reye’s syndrome, alcoholic foamy degeneration

Yeh MM, Brunt EM. *Diagnostic Histopathology* 2008;14(12)586-597
Necessary features to diagnose steatohepatitis

**AASLD single topic conference NASH Atlanta, 2002**

- **Necessary components** – *must see*
  - Steatosis, Macro>micro, mainly zone 3
  - Mixed *mild* lobular inflammation
  - Hepatocyte *ballooning*, most apparent near steatotic cells

- **Usually present, not necessary for diagnosis** – *often see*
  - Mallory’s hyaline, usually zone 3
  - Perisinusoidal fibrosis (zone 3)
  - Glycogenated nuclei (zone 1)
  - Lipogranulomas (usually small)
  - Occasional apoptotic hepatocytes/PASD+ve Kupffer cells

- **May be present, not necessary for diagnosis** – *may see*
  - Mild siderosis,
  - Megamitochondria

- **Not present in NASH** – *don’t see* = *something else as well*
  - Consider other causes of liver disease

Unusual for NASH, consider other causes of liver disease instead/as well

- Sclerosing hyaline necrosis
  = severe pattern of steatohepatitis seen in alcoholic liver disease

- Portal inflammation > lobular inflammation in early stage disease
- Lymphoid aggregates, plasma cells

- Significant eosinophils, granulomas
- Portal/periportal fibrosis much greater than zone 3 fibrosis
- Lobular disarray

- Acute cholestasis, bile plugs
- Chronic cholestasis, copper associated protein

- Significant iron, evidence of alpha 1 antitrypsin deficiency

_Hepatology. 2003 May;37(5):1202-19._
Staining for keratins 8/18 improves detection of hepatocyte injury in NAFLD

- More sensitive and specific for fibrogenic hepatocellular injury than H&E staining

- 40 biopsies from NASH CRN database study for no steatohepatitis (18): suspicious (7): definite (15) steatohepatitis

Results:

- 2 NASH weren’t
- 5/7 suspicious were no-NASH
- Improved inter-observer agreement on NASH
- Correlates with insulin resistance

Guy CD et al. Human Pathology 2012;43;790-800
How much portal inflammation/fibrosis in steatohepatitis?

When to suspect an additional cause of chronic liver disease?

• Clinicians suspect –
  – another cause of liver disease in liver screen, e.g. Autoantibodies, high ferritin, cholestatic LFTs
    ? Look for features of these in the biopsy
    Up to 30% NAFLD have liver autoantibodies, usually low titre

• Pathologists suspects –
  – Disproportionate portal tract inflammation, definite interface hepatitis
    ? Ask about autoantibodies, Ig level, hepatitis C
  – Any copper associated protein in non-cirrhotic biopsy
    ? Ask about autoantibodies, cholestatic liver function tests

• Portal inflammation in NASH is predictor of fibrosis progression
Can the pathologist distinguish ASH from NASH?

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<td>Glycogenated nuclei</td>
<td>More steatosis v. other features</td>
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How bad is it?

Stage:

1 perisinusoidal (1a, 1b) or periportal (1c)
2 peri-sinusoidal and portal/periportal
3 bridging fibrosis
4 cirrhosis

How bad is it? NAS activity score (0-8)

grade = sum of steatosis, lobular inflammation and ballooning

- Steatosis (0-3)
- Lobular inflammation (0-3)
- Hepatocyte ballooning (0-2)

Make diagnosis of steatohepatitis first,
Then grade severity
(not use activity score to make diagnosis of steatosis v steatohepatitis)

But not necessary in routine practice

Scoring system for evaluation of liver lesions in morbidly obese patients

Steatosis, Activity, Fibrosis (SAF) score
- Steatosis (0-3), Fibrosis (0-4), scored as NASH-CRN (Kleiner 2005)
- Activity score = combined scores for ballooning (0-2) and inflammation (0-2)
- Activity score ≥2 closely correlated with original histological diagnosis of NASH, and with serum AST and ALT and fibrosis

Bedossa P et al  Hepatology 2012;56;1751-1759
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Natural history of NASH:

Initially steatosis – protective, non-progressive

May → Metabolic cell injury – hepatocyte damage and senescence

Increasing fibrosis and nodular regeneration, decreasing steatosis

Bedossa P et al  Hepatology 2012;56;1751-1759
Non-alcoholic fatty liver disease (NAFLD): summary of NICE guidance

BMJ paper

BMJ 2016;354:i4428 doi: 10.1136/bmj.i4428 (Published 7 September 2016)
NICE and fatty liver

• Lack of national guidance and care pathways
• Investigation and referral of suspected NAFLD vary widely.
• Non-alcoholic fatty liver disease (NAFLD) is a spectrum of disease from fatty liver to non-alcoholic steatohepatitis, fibrosis and cirrhosis
• ~ 5-6% of patients with NAFL progress to non-alcoholic steatohepatitis (NASH), fibrosis or cirrhosis
• Diagnosing *NAFLD*

The **gold standard** for diagnosis of NAFLD is *liver biopsy*, which is **too high risk to be considered routine** in a population of patients who are likely to be asymptomatic and remain asymptomatic

• No evidence to support non-invasive testing for NAFLD in adults in general

• Routine LFT are not sensitive for the detection of NAFLD
NICE

• NAFLD is more common in people with:
  – Type 2 diabetes or
  – Metabolic syndrome.

• Take an alcohol history

• Advise NAFLD to keep taking statins.

• Consider stopping statins only if liver enzyme levels double within three months of starting statins – even with abnormal baseline
NICE — Assessing NAFLD for advanced liver fibrosis

- No strong evidence to support a specific non-invasive test for identifying NASH in NAFLD
- Severe fibrosis, poor prognosis
- Enhanced Liver Fibrosis (ELF) blood test most cost effective [Hyaluronic acid, Procollagen III, Tissue inhibitor of metalloproteinase 1]
- **DIAGNOSE** advanced fibrosis (ELF>10.5) in NAFLD [very low to low quality evidence!] & Refer hepatology
- Offer **RETESTING** every 3 years to >10.51
- **REASSURE** <10.51 no significant fibrosis, repeat 3 yrly
NICE — monitoring those with advanced fibrosis

- Monitor adults with NAFLD and advanced liver cirrhosis in line with NICE’s cirrhosis guideline
  
  Varices surveillance every 3 years
  Bone density every 2 years
  HCC screen – USS +/-AFP every 6 months
NAFLD is a risk factor for non-liver conditions

- Type 2 diabetes,
- Hypertension
- Chronic kidney disease

People with type 2 diabetes, NAFLD is a risk factor for:

- Atrial fibrillation
- Myocardial infarction
- Ischaemic stroke
- Death from cardiovascular causes
The spectrum of fatty liver disease

Case 1. NAFLD, diagnosis, severity, additional diagnosis

Case 2.
Leeds case 2: Ms SB – born Aug 1981

- 2010 – polyarthralgia, mostly normal LFT, biopsied elsewhere, near normal, but AMA positive
- 1/17 – referred for liver transplant assessment, diagnosis PBC
- Jaundice and Ascites, spider naevi
- Bilirubin 352, albumin 25, ALT 16, ALP 1.2 x ULN, INR 3, UKELD 66, MELD 31, Childs C 14
Ms SB continued

- AMA 1/1,000, M2 positive
- Clinical picture not fully in keeping with PBC, variable, but not high alcohol intake to help pain with joints – plan Trans jugular liver biopsy to ensure no other process
- Liver biopsy
Case 2  Female 35 years
Patient with immune mediated disease including Sjogrens and is AMA +ve, M2 type. Now presented with decompensated liver disease.

Clinically not fully in keeping with PBC alone and also variable intake of alcohol to ease pain from arthritis.
To rule out other cause for liver disease before transplanting urgently.
Case 2
Case 2
Case 2 – previous biopsy from 2007
Case 2 – previous biopsy from 2007
Case 2

Van Gieson
Case 2

Cam5.2

Keratin 8/18
Ms SB continued post bx

• Alcohol assessment

No clear history, variable answers, heaviest alcohol 2011 - 1 bottle of wine alternate days, recently low strength wine ½ bottle 7% alternate days

No other risk factors for fatty liver disease

Advised complete abstinence

• follow up – sepsis, palliative care, high alcohol intake confirmed
Can the pathologist distinguish ASH from NASH?

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The spectrum of fatty liver disease

Case 1. NAFLD, diagnosis, severity, additional diagnosis

Case 2. Alcohol related liver disease

Case 3.
Leeds Case 3: Ms JC Feb 1980

• 10/12 – dermatology clinic, noted to have abnormal LFT

Photo therapy 2008/9, then lost to follow up

• Poorly controlled psoriasis, plan therapy with methotrexate or biologics

Elevated PIIIP, abnormal LFT, fatty liver on USS

Rx ciclosporin – best to avoid methotrexate
Case 3  Female 33 years  
Past medical history of psoriasis.  
Unresponsive to fumeric acid esters.  ? for methotrexate
Case 3
Case 3
Leeds Case 3: Ms JC Feb 1980

JC continued to be monitored, but ciclosporin not effective

• 9/13 reconsider methotrexate

No alcohol, but plan liver biopsy in view of deranged LFT and fatty liver on USS
Leeds Case 3: Ms JC Feb 1980

- 7/15 – deranged LFT 4 years, ALT up and down, normal to 184
- Ferritin elevated 508
- BMI 34
- Troublesome cutaneous psoriasis
- Methotrexate for several years (possibly incorrect?), also Ciclosporin and biological agents - secukinumab
- No alcohol
Ms JC Feb 1980

- BARD score low – 1
- NAFLD score – low

SMA positive, elevated IgG 17
NILS otherwise negative

- USS fatty liver
Consider Fibroscan – but does not answer questions:

- Is there steatohepatitis associated with the methotrexate therapy?
- Is there early fibrosis? (Cirrhosis should be picked up on Fibroscan)

Liver biopsy would influence therapy decisions

- Is there auto immune hepatitis?
- Is there DILI?

Plan liver biopsy
Secukinumab toxicity

- Livertox database: [https://livertox.nih.gov/](https://livertox.nih.gov/)

Secukinumab is a human monoclonal antibody to interleukin-17A

Secukinumab in 3000 patients with psoriasis, deranged LFT no more than with placebo

Because of its immunomodulatory activity, secukinumab might induce an autoimmune reaction against hepatocytes – not yet seen
Case 3: 35 years female. 2 years later, second biopsy
Psoriasis - was previously on methotrexate and cyclosporin, now stopped because of raised ALT.
Had liver biopsy 2 years ago and did not show steatohepatitis or fibrosis. Hyperthyroidism, BMI 34, raised ALT, +ve SMA and slightly raised IgG. Recent Secukinumab therapy (anti IL17A)

US - fatty liver. ? autoimmune, ? drug induced. Biopsy to determine if further methotrexate therapy is reasonable? Can Secukinumab therapy continue?
Case 3 – second biopsy after 2 years
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Keratin 8/18
Fatty liver disease: alcohol, non-alcoholic, also drugs causing fatty liver disease

• Cause steatohepatitis directly
  – Amiodarone, irinotecan, methotrexate

• Promote steatohepatitis in patients with other risk factors
  – Tamoxifen, methotrexate, steroids,

• Association with steatosis
  – Steroids, 5FU, Brufen, anti-TB drugs, spironolactone,.......

Ramachandran R & Kakar S. J Clin Pathol 2009;62;481-492
JC continued

• No contraindication to methotrexate, but fatty liver is a risk factor

• Secukinumab effective, no clear contraindication

Patient lost to liver follow up - Secukinumab continued in dermatology clinic

• Deranged LFT persist
Methotrexate

How to untangle the conundrum?

Good for psoriasis
Bad for some livers
Methotrexate: 21 biopsies

• Brief review of previous 21 biopsies in whom methotrexate was entered into clinical details
• 5 miscellaneous – previous methotrexate therapy not the issue

Review of 16 biopsies for whom methotrexate was predominant issue

• Deranged LFT in 11
• High Fibroscan or PIIIP in 5
Methotrexate: 16 biopsies

• Cirrhosis in 2, stop methotrexate
• Steatosis mild to severe in all remaining
• Fibrosis and steato hepatitis in 2, therefore stop methotrexate
• Steatohepatitis, no significant fibrosis in 2 leading to cessation
• Others continue, but annual Fibroscan recommended
Methotrexate toxicity: generalisations

• Good evidence that methotrexate can be toxic to the liver, as with all fatty liver disease, effect, severity and outcome is highly variable and difficult to predict.

The larger the dose, the worse the effect.

Cirrhosis can occur, but is infrequent.

Cofactors appear to exacerbate toxicity, - alcohol excess, obesity and diabetes.

Standard LFT can provide false reassurance.

• PIIIP monitoring has proponents, but it is not perfect.
Methotrexate toxicity – Aithal et al 2011

• Clear association Methotrexate and liver toxicity, - dose, frequency, duration increase risk

• bridging fibrosis 0% after 1,500 mg
2.6% at 3,000 mg
8.2% at 6,000 mg

• Daily dose x 4 risk

• Wkly20mg 0 – 4% cirrhosis v >20mg 3 – 26%
Meta analysis finds the quality of studies is so poor that few conclusions are possible, other than liver biopsy is the most accurate means of determining damage.
Discussion re Mtx Rx initiation

- Risk factors, irrespective of LFT
  
  BMI >28
  Alcohol > 14 units
  Abnormal lipids
  Diabetes
The spectrum of fatty liver disease

Case 1. NAFLD, diagnosis, severity, additional diagnosis

Case 2. Alcohol related liver disease

Case 3. Drug induced liver injury

Case 4:
Leeds Case 4: BT aged 44

- Psoriatic arthropathy, found to have palmar erythema, low platelets and abnormal clotting
  Methotrexate therapy and etanercept – Methotrexate for 10 years, 25mg per week with folic acid
- LFT x 40, over 12 years, always normal
  Liver aetiology screen ANA +ve, IgG normal
- Previous Graves disease
- Several years of adalimumab
BT aged 44

- No risk factors, no obesity BMI 21.5, no alcohol excess – 1 drink every two months. Not diabetic
- No PIIIP results – PIIIP not favoured in RA, because of low specificity of high results
- Total dose of methotrexate 10.5g over 10 years

Can she have chronic liver disease and can it be due to methotrexate?

Biopsy:
Case 4  Female 44 years.
Rheumatoid arthritis. Deranged LFTs, ? source.

From accompanying clinic letter - patient has been taking methotrexate for 10 years at 25mg per week for 6 years then 15mg per week for 4 years. Normal liver function tests, and normal BMI, presented with low platelets and stigmata of chronic liver disease. Liver screen - positive ANA, nil else.
Case 4

Van Gieson

Keratin 8/18
BT aged 44

- No risk factors, no obesity BMI 21.5, no alcohol excess – 1 drink every two months. Not diabetic
- No PIIIP results – PIIIP not favoured in RA, because of low specificity of high results

Can she have chronic liver disease and can it be due to methotrexate?

Biopsy = inactive cirrhosis, no steatosis or Mallory bodies

Clinically = no other reason to have chronic liver disease. Methotrexate cumulative dose sufficient.
The spectrum of fatty liver disease

Case 1. NAFLD, diagnosis, severity, additional diagnosis

Case 2. Alcohol related liver disease

Case 3. Drug induced liver injury

Case 4: late stage liver disease, cirrhosis
The spectrum of fatty liver disease

Case 1. NAFLD, diagnosis, severity, additional diagnosis

Case 2. Alcohol related liver disease

Case 3. Drug induced liver injury

Case 4: late stage liver disease, cirrhosis
Variation in liver biopsies on my desk.....
Biopsies in the UK are highly variable.

A biopsy interpretation can only be as good as the specimen allows.
Biopsies in the UK are highly variable.

A biopsy report can only be as good as the specimen allows.

Needs 16G needle, and 20mm core for adequate sample.
Biopsies in the UK are highly variable.

A biopsy report can only be as good as the specimen allows.

Needs 16G needle, and 20mm core for adequate sample. *

Possible to have a great sample every time.

* Kleiner D & Bedossa P. Gastroenterology 2015:149:1305-1308
Liver histology and clinical trials for non-alcoholic steatohepatitis – perspectives from 2 pathologists

- Fibrosis is most important
- Needs adequate biopsy – 16G, >20mm
- NAFL and NASH are a dynamic continuum

Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with non-alcoholic fatty liver disease

* Kleiner D & Bedossa P. Gastroenterology 2015:149:1305-1308

Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with non-alcoholic fatty liver disease

Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up

**Figure 1.** Survival free of liver transplantation grouped by NASH and non-NASH and separated by the presence or absence of fibrosis (Fib). Survival free of liver transplantation was similar in patients without fibrosis and similar among patients with fibrosis regardless of whether or not they have a diagnosis of NASH (Supplementary Table 6).


The UK Liver Pathology Group (UKLPG) was formed in 2016 with the purpose:

To promote excellence in liver histopathology services in the UK and Ireland, across all levels of specialisation, through professional collaboration in education, quality assurance and research.

- This year’s CPD activities
- Liver CPD archive (activities 2006-2016)
- UK Liver Pathology EQA Scheme
- Reference images for liver biopsy reporting
- UKLPG - background and UKLPG committee meetings
- UKLPG - membership + how to join UKLPG
- Subcommittees
- Liver transplant pathology
- Paediatric liver pathology section
- Other professional documents
- Links to other sites

http://www.virtualpathology.leeds.ac.uk/eqa/specialist/liver/index.php
UK Liver Pathology Group – slides for this meeting

Email from Clare

20 on Tues, 37 on Weds

...............and 49 views on Thursday
average <2 mins
Example Reference Images
- steatosis

mild

Mild/moderate

moderate

Moderate/severe

severe

Example Reference Images - fibrosis

None/early

Bridging/Late

Early

Late

Early/Bridging

Bridging

Fleiss’ Kappa Score with 95% Confidence Intervals
Biopsies with fatty change

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Summary

Can’t biopsy everyone with fatty liver disease......
Not every obese patient has fatty liver disease

Purpose of biopsy: guide clinical management when non-invasive tests are insufficient:
- clinical question must be on the request form

1. Establish diagnosis – necessary features present
   +/- features of other disease
2. and assess severity – stage fibrosis (not = Ishak)
   - grade - steatosis
   - inflammation/ballooning (K8/18)
3. Consider aetiology – needs clinical information
   especially alcohol history
• The end