Evolving role of liver biopsy

• Introduction
• Reasons to NOT biopsy
• Reasons FOR a biopsy in known disease:
  – Staging of disease
  – Guide management – presence of SH, interface activity
  – Not responding to therapy
• Diagnostic uncertainty/ unknown disease
  – Problems of dual pathology
  – Atypical presentation
• Questions to address in main disease categories
• Summary
Introduction

• Jaundice mentioned in 3000BC
• Hippocrates – first use of term icteric
• Middle ages detail histories of epidemics
• 1923 First percutaneous liver biopsy (Germany)
• 1940s & 50s realisation of 2 types of transmissible hepatitis
• 1950s Menghini aspiration needle
Intro – rapid hepatology advances

• 1963 Australia antigen discovered, leading to Hepatitis B virus identification in 1967 & a vaccine 1969
• 1964 First liver transplant in UK
• 1978 Trans-jugular approach for liver biopsy
• 1980 description of Non Alcoholic Steatohepatitis, prominence in mid 1990s, term NAFLD in 2002.
Reasons for biopsy - Historical

• Biopsy initially taken for **diagnosis** in jaundice or deranged LFTs

• **Patterns** of injury indicated portal/ biliary or parenchymal; acute or chronic

• With recognition of chronic viral hepatitides, biopsy for **grading and staging** of disease

• Always a role for masses

Diagnosis made but little treatment options
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But now no need for biopsy...

- Most viruses diagnosable on serology and/or PCR
- Most viruses amenable to treatment or prevention – vaccination, high sustained viral response with modern direct-acting anti-viral agents
- Fatty liver disease striking increase, obvious risk factors
- Serological parameters for assessing stage and grade of chronic liver disease
- Liver stiffness for assessing fibrosis
- Genetic testing for metabolic diseases, quantitative studies and imaging
- Biliary disease diagnosable on Ab serology and radiology; increase in 2nd order antibodies (line blot testing) important in all autoimmune conditions
Report on liver biopsy should not simply state *consistent with* the diagnosis given in clinical information.
So...Why else not to biopsy?

- Liver biopsy has always been regarded as the **Gold Standard** (everything! fibrosis, inflammation, steatosis, disease presence or absence)
  **BUT tarnished, gilt plated** at best, limitations of sampling error (disease process and specimen adequacy) and intra- and inter-observer variability.

- Safe but as an invasive procedure not without risk
  - Pain 30%, bleeding 2-3%, death 0.01%-0.33% - greater in focal lesions, cancer, abnormal clotting and historical cohorts

- WHO launched No Hep – aiming to eliminate viral hepatitis as a public health threat by 2030

What about the UK?
Liver Disease mortality a real and steady increase in UK.

Liver Disease 3rd most common cause of premature death; most deaths 50-59yrs (life expectancy of 84yr)
Alcohol related Liver Disease

• Nearly 10 million adults in England have drinking habits potentially harmful.
• Difficult to separate from NAFLD, risk factors.
• May be denied, so harder to establish clinically.

Figure 1: Summary of weekly alcohol consumption, 2017
Note: Aged 16 and over.

<table>
<thead>
<tr>
<th></th>
<th>Non-drinker</th>
<th>Up to 14 units (low risk)</th>
<th>More than 14, up to 35/50 units (increasing risk)</th>
<th>More than 35/50 units (higher risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>16%</td>
<td>56%</td>
<td>24%</td>
<td>4%</td>
</tr>
<tr>
<td>Women</td>
<td>21%</td>
<td>64%</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>All adults</td>
<td>19%</td>
<td>60%</td>
<td>17%</td>
<td>4%</td>
</tr>
</tbody>
</table>
NAFLD - WHO figures, based on BMI

• In 2016 >1.9 billion adults were overweight; over 650 million were obese.
• In 2016, 39% of adults (39% of men and 40% of women) were overweight.
• Overall, about 13% of the population (11% of men and 15% of women) were obese.
• Worldwide prevalence of obesity nearly tripled between 1975 and 2016.

between 1975 and 2016.
Why not to biopsy - Non-invasive markers of Fibrosis

• Degree of fibrosis predicts morbidity and mortality; portal hypertension, cirrhosis & liver failure, HCC.

• Various methods of assessing liver stiffness by elastography - Fibroscan, ARFI, MRE - validated in common diseases; good or ruling out fibrosis or ruling in advanced fibrosis but limited ability in the middle.

• Serum biomarkers – ELF, Fibrotest, FIB4, APRI, Fibroindex (common markers, age, tissue breakdown and inflammation and complex formulae) - limited ability in the middle

But helps stratify/ triage those requiring biopsy
Fibroscan
Scale of measurements for known diseases

- Reading is converted into 5 stage fibrosis score F0-4
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53 yr ♀; deranged LFTs - ↑ALT 3yrs, now in 90s
PMH PsA on secukinumab, psoriasis, Klinefelter syndrome, asthma, dyslipidaemia, OA, BMI 35.49

USS - fatty liver, normal PV, spleen. No ascites

Fibroscan Elastography score: 12.9 kPa = F4

Mismatch of clinical and non-invasive assessment – decision to biopsy

Ballooning and tiny Mallory-Denk bodies, fat & inflammation = steatohepatitis

Presence of steatohepatitis currently not assessable by other means Important for progression.
Pericellular fibrosis, zone 3

No bridging, minimal portal

Staging by description or scores – NAS (Kleiner) or SAF (Bedossa); with trails of treatment, possibly more biopsies and more numbers
Fibroscan - Possible Confounders

- Factors altering depth of liver in relation to probe eg BMI
- Factors altering viscoelastostatic properties eg inflammation, steatohepatitis (bx remains gold standard)
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Little portal, lobular or interface inflammation; duct loss
Not responding to therapy

Prominent ductopenia, CAP +++, little fibrosis or ductular reaction. Ductopenic variant of PBC

Japanese staging gives good prognosis, including urso response,

Nakamura Hepatology Res 2015
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Dual Pathology

• In 2017, 1.11 billion prescription items were dispensed in the community. *(NHS Digital England)*

• With attendant co-morbidities

• In 2017-8, **62%** of adults overweight or obese in England. *(Public Health England)*

• alcohol

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**Figure 1: Summary of weekly alcohol consumption, 2017**


*Note: Aged 16 and over.*
When could there be a 2\textsuperscript{nd} pathology?

- Natural history or complication of the disease
- Same risk factors for other diseases
- Related to the treatment of that disease
- Genetic abnormalities common within the population
- Potential injurious agents common in the population
- Totally incidentally
29yr, 13yr h.o
IBD, 3yr ago
MRCP - PSC;
now raised ALT and AP.
65♂ HCV+ve, also chronic lymphocytic leukaemia. Hepatosplenomegaly. ?secondary to CLL or hep C.
Multiple possible causal factors

46 ♂ metastatic melanoma receiving immunotherapy. Deranged LFTs. ?immune related vs malignant infiltration
Consequences of more than one diagnosis

- Different treatment strategies – overlap, venesection iron
- Different follow-up strategies – clear HCV or HBV but still with N/AFLD; family members
- Symbiotic effect of more than one ‘hit’ to accelerating CLD, decompensation and HCC
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63♀ AST 59, ALP 262, ASMA +ve, AMA –ve (including extended panel).

Duct inflammation, ductopenia & cholate stasis
AMA negative primary biliary cholangitis
Liver biopsy reporting

• Adequacy, adequacy, adequacy
• Ample evidence under-stage and under-scoring if specimen too short and/or narrow, esp. for portal based disease, (viral hepatitis and NAFLD)
• Need > 20mm (30mm for AASLD guidelines) and of 16 gauge needle ~1mm
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• Indications for liver biopsy are changing; more complicated clinical scenarios and less common diseases.

• Don’t state – ‘consistent with’ proffered diagnosis - address the clinical question.

Are all the features explicable by the known diagnosis.

Clinico-pathological communication essential for helpful report.
Role of liver biopsy in Biliary disease

- Limited; radiology paramount for large duct disease
- To diagnose small duct PSC
- To diagnose variants of PBC – accelerated ductopenia, early PHT, AMA negative
- To assess if a component of autoimmune hepatitis exists and how much.
- To stage the disease, especially if other risk factors for CLD (NAFLD)
Role of Liver biopsy in ArLD

- Acute setting of jaundice - ? Alcholic hepatitis, ? Decompensation ? Other (esp. sepsis), drugs
- If Alc Hep, prognostic information
- To confirm abstinence???
Role of liver biopsy in NAFLD

• To clarify stage of fibrosis when not clear/discrepant from non-invasive markers.
• To establish if steatohepatitis is present; stratify for trails and treatment.
• Risk factors v. common, so may be masking another aetiology.
• When dual pathology present to identify dominant pattern of injury.
• Follow up in trail setting.
Role of liver biopsy in DILI

- Are changes compatible with such a diagnosis?
- Is this a known pattern?
- Prognostication – severity of hepatitis, regeneration, degree of duct damage or ductopenia?
- Is there DILI in addition to underlying chronic liver disease?
Liver-tox screen

SEARCH THE LIVERTOX DATABASE

Search for a specific medication, herbal or supplement:

Browse by first letter of medication, herbal or supplement:

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

LIVERTOX® provides up-to-date, accurate, and easily accessed information on the diagnosis, cause, frequency, patterns, and management of liver injury attributable to prescription and nonprescription medications, herbs and dietary supplements. LIVERTOX also includes a case registry that will enable scientific analysis and better characterization of the clinical patterns of liver injury. The LIVERTOX website provides a comprehensive resource for physicians and their patients, and for clinical and basic science researchers and specialists.
Role of liver biopsy in Autoimmune hepatitis

• Are the features compatible on initial presentation, how active
• Is there underlying chronicity, how much fibrosis
• Are there other, biliary features
• Is there histological remission prior to stopping treatment
• Is any change in biochemistry due to flare of disease, or is there 2nd pathology eg NAFLD, DILI or virus.

Get an expert opinion – have Prof Stefan Hubscher on fast-dial