Patterns of abnormal LFTs and their differential diagnosis

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Outline

• liver function tests / tests of liver function
• sources of various liver enzymes
• patterns of liver enzyme abnormality
• major causes of abnormal liver function
• Assess liver disease severity
• Form a differential diagnosis on the basis of LFTs and limited history
Liver function tests

- AST
- ALT
- alkaline phosphatase
- GGT
- Bilirubin
- Albumin, total protein.

— ie mostly indicators of liver damage
Tests of liver function

• Synthetic functions:
  – Albumin
  – Clotting factors – prothrombin time

• Excretory function
  – bilirubin
Interpretation of LFTs

• AST / ALT – hepatocellular enzymes
• AST – mitochondrial
• ALT – cytosolic
• AST / ALT ratio
  – ALT > AST – hepatitis
  – AST > ALT – alcohol or in advanced fibrosis / cirrhosis
Interpretation of LFTs

- Alkaline phosphatase – biliary epithelium
  - also comes from bone
- GGT – also biliary
- Alk P ↑  GGT ↑  - biliary source
  - Obstruction
  - Infiltration
  - congestion
- Alk Phos ↑  GGT normal  - think bones
- Isoenzymes – rarely needed
Interpretation of LFTs

- Albumin
- Total protein / globulin fraction

Other tests:

- PT / INR
- Alpha-foetoprotein (AFP)
- Full blood count
Causes of chronic liver disease

- Non-alcoholic fatty liver disease
- Alcohol
- Viral
- Immunological
- Genetic / Metabolic
Investigation of abnormal LFTs

- History

- Non-invasive liver disease screen

- Imaging – typically ultrasound
Investigation of abnormal LFTs

• History
  – alcohol, drugs, sex, blood, travel, PMH, FH

• Non-invasive liver disease screen

• Imaging – typically ultrasound
Investigation of abnormal LFTs

• Viral markers
  – HCV antibody (HCV Ab)
  – Hepatitis B surface antigen (HBsAg)

• HCV – 300,000 cases in UK
• HBV – 180,000 cases in UK
Investigation of abnormal LFTs

• Immunoglobulins
  – IgG    - auto immune hepatitis
  – IgM    - primary biliary cirrhosis
  – IgA    - alcohol
  – All 3  - cirrhosis

• Auto antibodies
  – ANA / ASM  - auto immune hepatitis (type I)
  – LKM       - auto immune hepatitis (type II)
  – AMA (M2)  - primary biliary cirrhosis
  – ANCA      - primary sclerosing cholangitis
Investigation of abnormal LFTs

- Haemochromatosis
  - Ferritin
  - Consider HFE genotype, transferrin saturation

- Alpha-1 anti-trypsin deficiency
  - A1AT level

- (Wilson's disease - copper / caeruloplasmin)
Chronic liver disease screen:

- HBsAg
- HCV Ab
- Ig’s and auto antibodies
- Ferritin
- A1AT
- AFP
- ± Caeruloplasmin / copper
Liver disease severity:

• Biochemical
  – Albumin
  – PT
  – Bilirubin

• Clinical
  – Ascites
  – Hepatic encephalopathy
  – Nutritional status
Child-Pugh score

- Child – Turcotte score – 1964
- Modified by Pugh 1973 – Child-Pugh score
- Useful predictor of outcomes
  - Death from variceal bleeding
  - Outcomes of surgery in patients with cirrhosis
  - Comparison of patients in different hospitals

*Pugh RN et al B J Surg 1973;60:646*
<table>
<thead>
<tr>
<th>Category</th>
<th>1</th>
<th>2</th>
<th>3</th>
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</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>0</td>
<td>I/II</td>
<td>III/IV</td>
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<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Mild / mod</td>
<td>Severe</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt;35</td>
<td>35-50</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt;35</td>
<td>28-35</td>
<td>&lt;28</td>
</tr>
<tr>
<td>PT prolongation</td>
<td>1-4 seconds</td>
<td>4-6 seconds</td>
<td>&gt;6 seconds</td>
</tr>
</tbody>
</table>

*Child’s A - 6 or less, Child’s B - 7 - 9,*

*Child’s C - 10 or more*
Pros / cons with C-P score:

• Very simple
• Easily calculated
• Good predictor

• Subjective measures
• “Ceiling” effect ie bili >300, alb 19 scores same as bili 65, alb 26
Other liver severity scores

• Used in transplant listing decisions

• MELD
  – INR / bilirubin / creatinine

• UKELD
  – INR / bilirubin / creatinine / sodium
Case 1

Liver biopsy
Miss KM, 21yrs
Jaundiced, abn LFTs
?cause
Case 1

• AST 1287, ALT 1860, Alk P 367, GGT 478, bili 182, alb 35, total protein 79
• Hb14.8, WBC 9.7, plts 296, INR1.2

• Severe hepatitis with jaundice but preserved liver synthetic function
• Aetiology:
  – ?viral
  – ? Auto-immune
  – ??drug toxicity
Case 2

Mr J D
Age 49
EtOH++
Abn LFTs? Cause
Case 2 - Mr JD

AST 497, ALT 563, Alk P 203, GGT 1378, bili 87, alb 37, total protein 65
Hb15.8, WBC 6.4 plts 296, INR1.2

• Hepatitic process with mild jaundice
• Preserved liver synthetic function
• AST/ALT wrong
• Transaminases too high for alcoholic hepatitis
• Think additional pathology
  – Viral, auto-immune, drugs
Case 3

Mrs SB Age 63
Type II diabetic, overweight
no alcohol
Persistent mildly abnormal LFTs ? cause
Case 3 - Mrs SB

- ALT 57, AST 84, bili 17, Alb 36, Alk P 107, GGT 167
- Hb 13.1, WBC 4.5, Plts 128
- NILS all normal / negative
Case 3 - Mrs SB

- ALT 57, AST 84, bili 17, Alb 36, Alk P 107, GGT 167
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- Likely diagnosis - NAFLD
- Concerns?
Case 3 - Mrs SB

- ALT 57, AST 84, bili 17, Alb 36, Alk P 107, GGT 167
- Hb 13.1, WBC 4.5, Plts 128
- NILS all normal / negative

- Likely diagnosis - NAFLD
- Concerns ?
  - AST / ALT wrong - ?cirrhotic ? Drinking
  - ↓ platelets may indicate hypersplenism
NAFLD fibrosis scores

• BARD – BMI, AST/ALT ratio, T2DM

• NAFLD Fibrosis score – age, diabetes, BMI, platelets, albumin and AST/ALT ratio

• FIB-4 – Age, AST / ALT

• All based on combinations of AST/ ALT ratio, diabetes, obesity, age and platelet count
  – predict presence of severe fibrosis, but all have limitations
Additional caveats

• Abnormal LFTs do not always indicate liver disease......

• Normal range is set by mean ± 2SD

• NHANES study of 3747 adults at low risk of liver disease
• ULN ALT 29 for men, 22 for women
  – 36.4% of men and 23.8% of women have abnormal LFTs!

Hepatology 2012;55:447
Additional caveats

- Normal LFTs do not always exclude liver disease.

- HCV – 1:6 with persistently normal ALT will have significant pathology on liver bx.

- Clear link between ALT elevation and liver mortality, even for values within the normal range.

- In a community setting 72% (71/98) with high Fibroscan score had normal LFTs.

References:

- Am J Gastro 2003;98:1588
- Gastro 2009;136:477
- Harman et al BMJ Open 2015;5:e007516
Conclusions

• Interpreting LFTs useful and easy
• Most liver diseases can be diagnosed and assessed by blood tests
• Exercise caution when interpreting numbers
• Liver biopsy still has a useful role......