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, weight gain, 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 – ?100,000 undiagnosed cases in UK
- HBV – ?180,000 cases in UK

Investigation of abnormal LFTs

- Immunoglobulins
  - IgG - auto immune hepatitis
  - IgM - primary biliary cholangitis
  - IgA - alcohol
  - All 3 - cirrhosis with portal hypertension
- Auto antibodies
  - AMA (M2) - primary biliary cholangitis
  - ANA / ASM - auto immune hepatitis (type I)
    - LKM - auto immune hepatitis (type II)
    - ANCA - primary sclerosing cholangitis

Investigation of abnormal LFTs

- Haemochromatosis
  - Ferritin and transferrin saturation
  - consider HFE genotype
- Alpha-1 anti-trypsin deficiency
  - A1AT level
- (Wilsons disease - copper / caeruloplasmin)

Chronic liver disease screen:

- HBsAg
- HCV Ab
- Ig’s and auto antibodies
- Ferritin and transferrin saturation
- 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

Child-Pugh score for cirrhosis severity

category	1	2	3
Encephalopathy	0	I/II	III/IV
Ascites	Absent	Mild / mod	Severe
Bilirubin	<35	35-50	>50
Albumin	>35	28-35	<28
PT prolongation	1-4 seconds	4-6 seconds	>6 seconds

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

Fibrosis severity scores

- FIB-4 – Age, AST / ALT

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

Fibrosis severity scores

- FIB-4
  - (age x AST)/(platelets x ((√ALT))
    - https://gps.camdenccg. nhs.uk/fib-4-calculator

- NAFLD Fibrosis score
  - 1.675 + 0.037 × age (years) + 0.094 × BMI (kg/ m2) + 1.13 × IFG/diabetes (yes=1, no=0) + 0.99 × AST/ ALT ratio – 0.013 × platelet (×109/L) – 0.66 × albumin (g/dL)
    - www.nafldscore.com

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

Case 1

- 21yr old female
- 2 weeks of progressive jaundice and abnormal LFTs

? Cause

? Needs a liver biopsy

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

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

- Acute hepatitis with jaundice but preserved liver synthetic function
- Aetiology:
  - ?viral ? Auto-immune ??drug toxicity

Case 2

- 49 year old male patient
- EtOH++
- increasingly abnormal LFTs

Does he need a biopsy?

Case 2

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

Case 2

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 for alcohol
- Transaminases too high for alcoholic hepatitis
- Think additional pathology
  - Viral, auto-immune, drugs

Case 3

- 63 year old female patient
- Type II diabetic, overweight
- no alcohol
- Persistent mildly abnormal LFTs

? Cause

? Severity of liver disease

Case 3

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

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
- Diagnosis?
- NAFLD
- Concerns ?

Case 3

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
- Diagnosis?
- NAFLD
- Concerns ?
  - AST / ALT wrong - ?cirrhotic ? Drinking
  - ↓ platelets may indicate hypersplenism

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

Am J Gastro 2003;98:1588

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

Gastro 2009;136:477

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

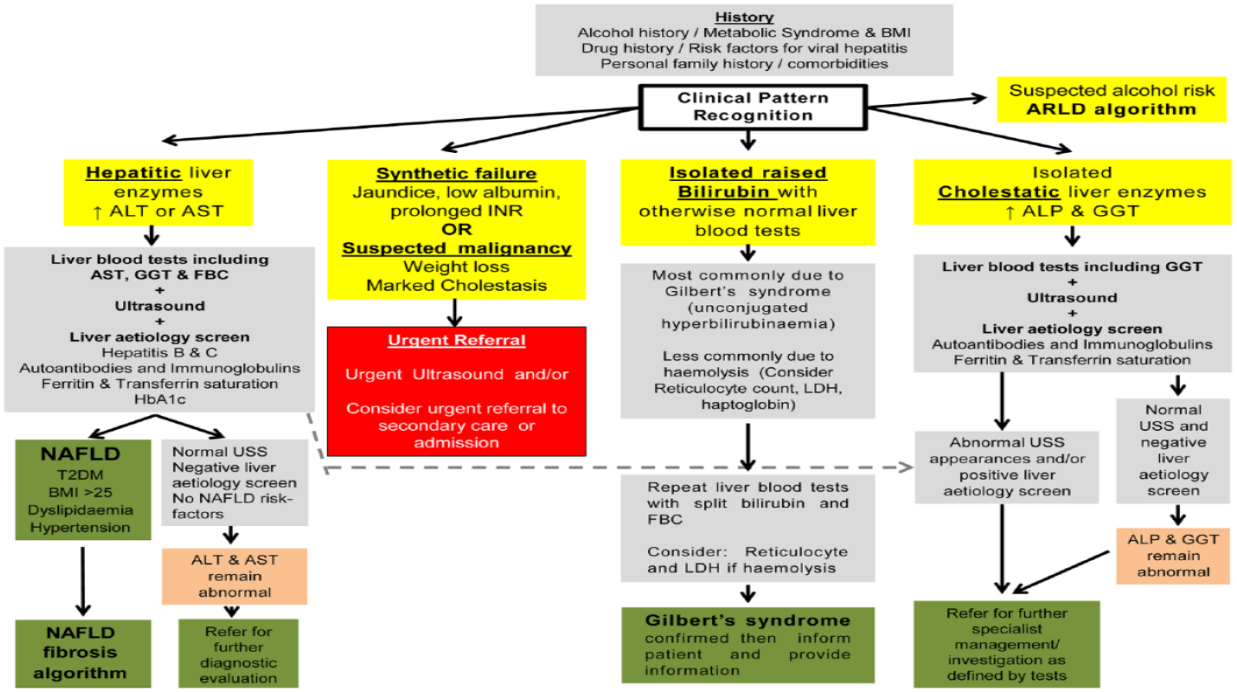
Harman et al BMJ Open 2015;5:e007516

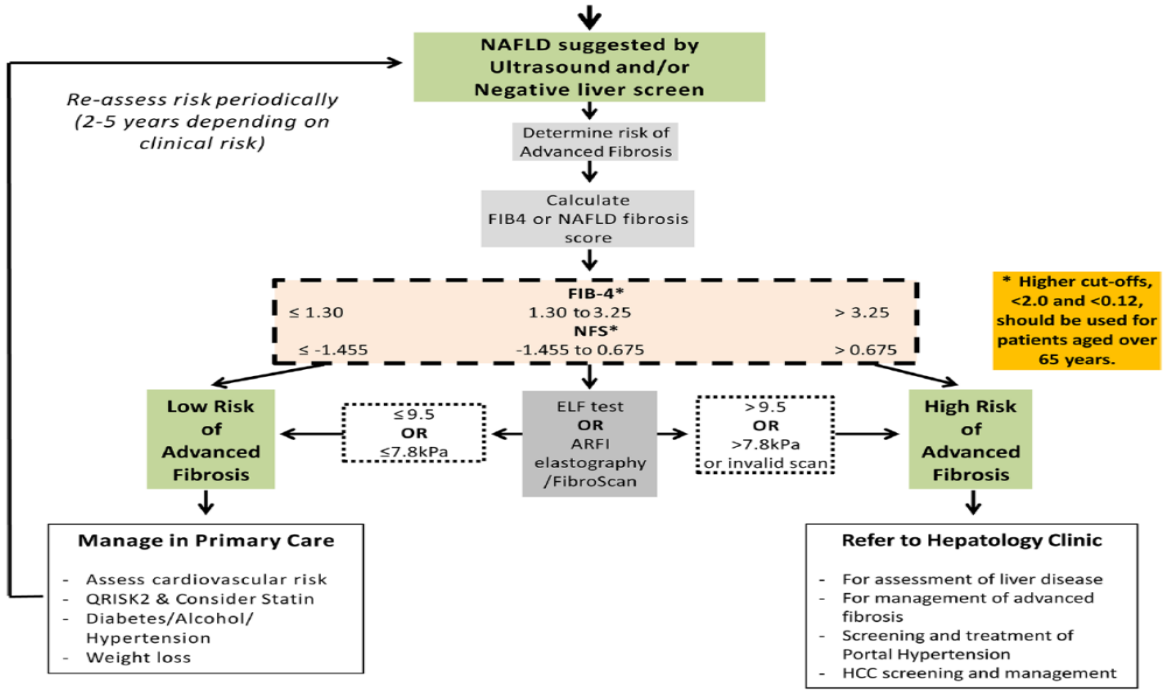
OPEN ACCESS

Guidelines on the management of abnormal liver blood tests

Philip N Newsome,[1,2] Rob Cramb,[1] Suzanne M Davison,[3] John F Dillon,[4] Mark Foulerton,[5] Edmund M Godfrey,[6] Richard Hall,[7] Ulrike Harrower,[8] Mark Hudson,[9,10] Andrew Langford,[11] Anne Mackie,[8] Robert Mitchell-Thain,[12] Karen Sennett,[13,14] Nicholas C Sheron,[15] Julia Verne,[8] Martine Walmsley,[16] Andrew Yeoman[17]

https://www.bsg.org.uk/resource/guidelines-on-the-management-of-abnormal-liver-blood-tests.html





Gut 2018;67:6-19.

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……