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Abnormal LFTs - a practical approach

Update on Liver Cancer GP Study Afternoon
Thursday 21st July 2016

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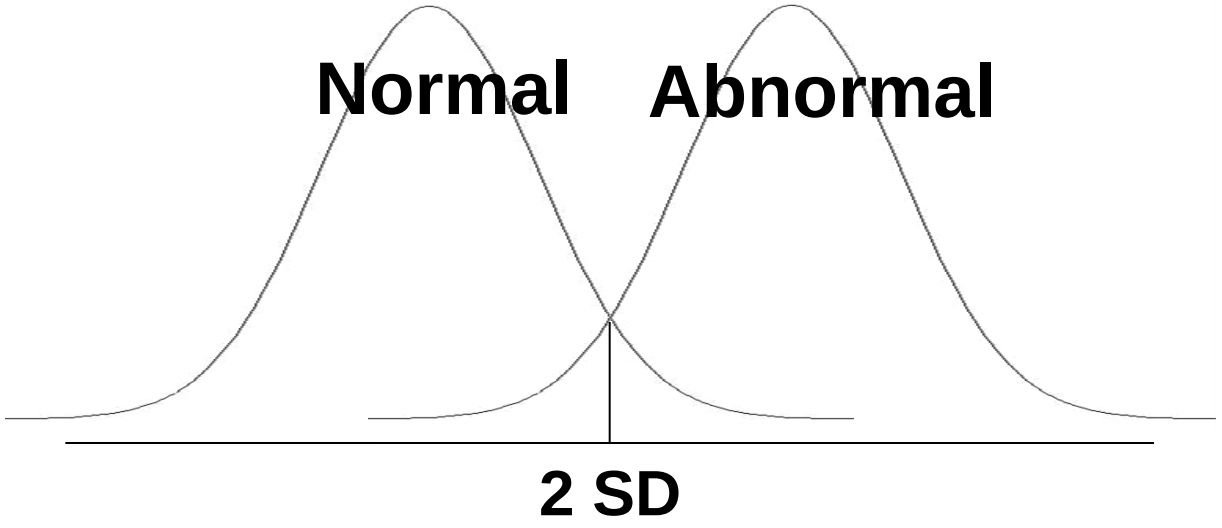
Do not interpret LFTs on their own

- History
- Clinical examination
- Laboratory findings
- Imaging

Liver function tests

- **Interpretation must be performed within the context of the patient's risk factors, symptoms, concomitant conditions, medications, and physical findings**
- **Rarely provide specific Dx, but rather suggest a general category of liver disease**
- **Differing laboratories → differing normal values**

Normal Laboratory Values



normal values = mean ± 2SD of normal population

LFT abnormalities classification

- Hepatocellular injury (AST, ALT)
- Cholestatic injury (ALP, γGT, bilirubin)
- Infiltration (ALP, γGT, occasionally bilirubin)
- Synthetic function (albumin, INR)

Albumin, INR, bilirubin – also used as prognostic factors (Child-Pugh, MELD, UKELD)

Aminotransferases

AST	ALT
catalyze transfer amino groups to form pyruvic acid	catalyze transfer amino groups to form oxaloacetate
cytosol (20%) and mitochondria (80%), predominantly periportal hepatocytes	cytosol
T1/2 12-22 hr	T1/2 37- 47 hr.
liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leucocytes, and RBC	low concentration in other tissues – more specific for liver disease than AST

Unexpected ALT elevation

- Muscle disease/injury (CPK, aldolase)

- Thyroid dysfunction (TSH)

- Coeliac disease (anti-endomysial antibody)

Alkaline phosphatase

- Of cytosolic origin in the liver
- Present in placenta, ileal mucosa, kidney, bone
- Half life = 3 days
- Elevated in 3d trimester of pregnancy
- Blood types O and B: can have elevated ALP after fatty meal due to influx of intestinal ALP
- Liver origin: elevated GGT

  Bone origin: normal GGT

Alkaline phosphatase

Physiologic

- **>60 yr.**
- **child and adolescent**
- **pregnancy**
- **blood group O**
- **post meal (fatty meal)**

Pathologic

- **intrahepatic**
- **extrahepatic**

γ-glutamyltransferase (GGT)

- catalyzed transfer of γ-glutamyl groups of peptides to other amino acid
- abundant in liver, kidney, pancreas, intestine, and prostate, spleen, heart, brain but not in bone
- T1/2
  - 7-10 days
  - 28 days in alcohol-associated liver injury

γ-glutamyltransferase (GGT)

- Increase
  - alcohol (even without liver disease)
  - drug
    - anticonvulsant (CBZ, phenytoin, and barbiturate), warfarin
  - almost all type of liver diseases, inc fatty liver
  - COPD, renal failure, DM, hyperthyroidism, RA, AMI, pancreatic disease

BALLETS (Birmingham and Lambeth Liver Evaluation Testing Strategies) study

- Prospective study in 11 GP practices Nov 2005 – Nov 2008
- Patients with no known liver disease and at least 1 abnormal liver function test
- Further assessment with:
  - History
  - Complete 'liver panel'
  - Ultrasound
- Follow up for 2 years

Results

- Armstrong et al J Hepatology 2011
- 1118 Birmingham patients

Reason for LFT testing

Table 1. The 10 most commonly recorded reasons for why the LFT's were undertaken by the PCP. Values are percentages (numbers). Percentages include all values (n = 1118). Other reasons accounted for 20.9% (234).

Documented reason	Percentage (n)
Diabetes review	18.0 (201)
Non-specific routine bloods	15.2 (171)
Hypertensive disease review	11.4 (128)
Gastrointestinal symptoms (excluding liver-specific)	10.0 (112)
Generalised fatigue or tiredness	6.2 (69)
Cardiovascular disease review	4.7 (53)
Medications review (non-specific)	4.5 (50)
Hyperlipidaemia disease review	3.8 (42)
Neurological symptoms (inc. confusion)	2.7 (31)
Musculoskeletal symptoms (i.e. joint pain)	2.4 (27)

Patient demographics

Characteristics	Total (n = 1118)
Median (IQR) age (years)	60 (48-70)
Gender	
Male	56 (628)
Female	44 (490)
Ethnicity (%)	
White	83.9 (938)
African-Caribbean	3.9 (44)
Asian/Arabic	8.1 (90)
Mixed/other	1.3 (15)
Unknown	2.8 (31)
Alcohol consumption cut-offs	
Abstinence	42.5 (475)
Mild	20.8 (232)
Moderate	10.5 (117)
At-risk	26.3 (294)
Metabolic Phenotypes	
Type 2 diabetes	23.5 (263)
Hypertensive Disease	43.2 (483)
Obesity	40.7 (455)
Median (IQR) measured BMI (Kg/m²)	28.7 (25.3-33.1)
Median (IQR) waist circumference (cm)	
Male	103 (95-112)
Female	96 (85-109)

Results

- Cause identified in 54.9%

Cause	Percentage (n)	GGT [U/L]	ALT [U/L]	AST [U/L]	ALP [U/L]	Bili [µmol/L]	Alb [g/L]
NAFLD	26.4 (295)	59 (41-88)	38 (27-54)	30 (23-40)	206 (167-266)	9 (6-12)	45 (43-47)
At-risk alcohol intake							
Non-Fatty liver	14.0 (156)	69 (46-115)	30 (22-44)	28 (22-35)	190 (159-238)	10 (7-13)	46 (44-48)
Fatty liver	11.3 (126)	81 (52-148)	46 (33-65)	36 (28-49)	178 (150-218)	9 (8-13)	47 (45-49)
PBC	0.81 (9)	99 (45-186)	15 (20-31)	27 (25-36)	396 (337-463)	7 (6-13)	43 (42-45)
HBV	0.72 (8)	53 (32-418)	92 (49-156)	62 (26-97)	184 (147-242)	8 (5-15)	46 (43-52)
Haemochromatosis							
Homozygote [C282Y or H63D]	0.54 (6)	73 (31-166)	59 (43-79)	39 (32-56)	202 (158-382)	8 (5-23)	46 (45-48)
Comp. heterozygote [C282Y + H63D]	0.36 (4)	56 (25-458)	51 (54-149)	25 (42-238)	121 (75-135)	12 (5-21)	51 (45-53)
Other (inc. cancer, drug, abscess)	0.36 (4)	85 (27-179)	29 (17-58)	31 (18-44)	273 (191-368)	12 (7-18)	44 (39-48)
HCV*	0.17 (2)	x (34, 452)	x (151, -)	x (101, 70)	x (514, 214)	x (8, 8)	x (48, 47)
PSC*	0.17 (2)	x (-, 600)	x (51, 212)	x (33, 124)	x (176, 990)	x (12, 10)	x (47, 46)
A1AD*	0.17 (2)	x (59, 62)	x (41, 50)	x (24, 25)	x (161, 138)	x (11, 12)	x (48, 50)
Unexplained group	45.1 (504)	56 (33-91)	26 (19-38)	26 (22-33)	202 (162-274)	9 (6-13)	45 (43-47)

- Viral, genetic or autoimmune disease in 3%

Assessing Patients with Abnormal LFTs

- Do they have liver disease?
- What type of liver disease?
- How severe is it?
  - 'Stage of disease'
  - How much liver fibrosis

Screening Investigations for Liver Disease

- Chronic Alcohol Abuse
- Hepatitis B
- Hepatitis C
- Other Liver viruses
- Autoimmune Hepatitis/Primary Biliary Cirrhosis/Primary Sclerosing Cholangitis
- Non-alcoholic Fatty Liver Disease (NASH)
- Haemochromatosis
- Wilson's disease (<40yo)
- Alpha1-Antitrypsin Deficiency
- Liver Tumours
- (Cystic fibrosis + other congenital diseases e.g. biliary atresia, LAL-Def, glycogen storage disease)

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- **DRUGS/DILI: single largest class of agents that cause idiosyncratic drug-induced liver injury**

Idiosyncratic drug-induced liver injury (DILI)

Semin Liver Dis 2014

- Cholestatic, or hepatitic, or more classically mixed
- Like other adverse effects of drugs, underreported and underestimated in most epidemiological studies based on registries
- Same probably true for prospective population-based studies
- Recent population based study: crude incidence of ~19 cases/100,000/yr
- Amoxicillin-clavulanate most commonly implicated (1/2,300 users)
- Azathioprine, Infliximab
- Significant statin-induced hepatotoxicity <1%
- Most DILI in children & adults - associated with antibiotics or anticonvulsants
- DILI with intravenous drugs shows no major differences from DILI due to orally administered agents
- **Dx of exclusion, +/- liver Bx, +/- trial of stopping (& restarting?) suspect drug**

Abnormal Aminotransferase Values of Unknown Cause: Proposed Algorithm for Primary Care Management/Referral to Hepatology Services.

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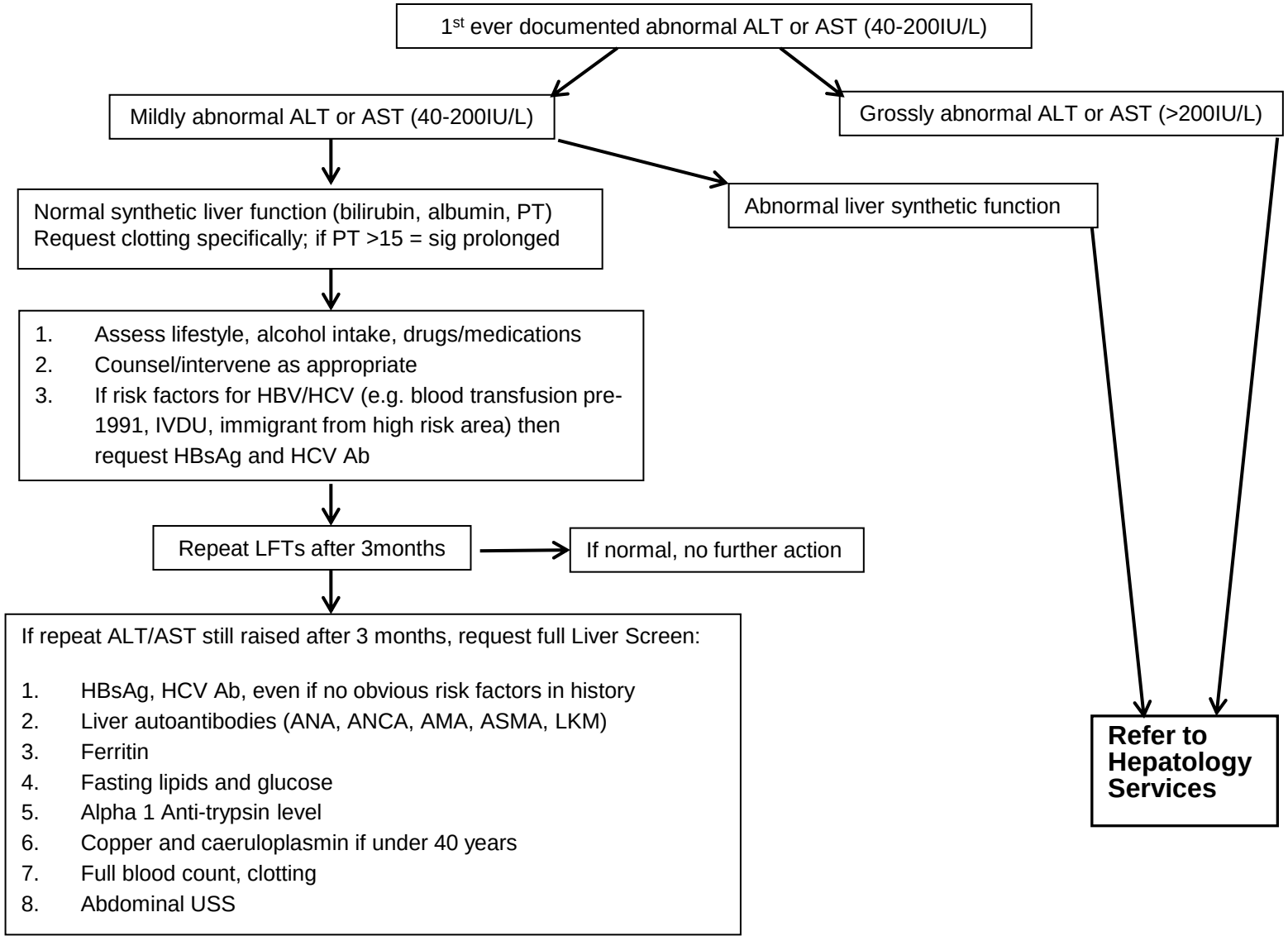

Fatty Liver Disease suspected?

1. USS suggests fatty liver
2. Liver Screen is negative

Address alcohol, diet, exercise, weight, lipids, glucose

Refer to Hepatology Services if <u>any</u> of the following:

- **All above tests negative/normal but ALT persistently raised > twice ULN or AST>ALT**
- **HBsAg or HCV Ab positive*(even if LFTs have normalised)***
- **Any liver auto-antibodies positive**
- **Ferritin > 500**
- **USS features of cirrhosis &/or portal hypertension (ascites, big spleen, low platelets)**
- **USS shows liver lesions**

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