Interpreting abnormal liver function tests

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Case study

- 18 year old Male
- Attends surgery with sore throat and signs of tonsillitis
- Also requesting antibiotic for acne as he had taken someone else’s medication whilst on holiday which had helped

- GP checks electrolytes and LFTs due to non-prescribed medication use
- LFTs grossly abnormal!
LFT results

• Bilirubin 14
• ALP 233 (normal range 30-130)
• ALT 230 (normal range 0-40)

• What are the possible causes of his deranged LFTs?

• What further questions would you like to ask and which further tests would you do?
Points to include in history

- Recent travel
- Transfusions
- Drugs, including paracetamol overdose and herbal remedies.
- Tattoos
- Unprotected sexual intercourse
- Alcohol
- Occupation
- Diabetes mellitus, Obesity, hyperlipidaemia (all associated with fatty liver disease)
- Family history
Further clinical history from patient...

- History of drinking excess alcohol on weekends
- Recent holiday to Egypt – also drank alcohol to excess at the time
Further tests requested

- FBC
- Repeat electrolytes and LFTs
- GGT
- Ferritin and Iron profile
- Glandular Fever screen
- Serum proteins
- EBV serology

- Clotting screen
- CRP
- Alpha-1- antitrypsin
- Glucose
- Hepatitis A IgM/IgG
- Hepatitis B and C screen
Results

- Hb 14.9
  - **wcc 15.1** (normal range 3.5-11)
  - Platelets 171
  - **mcv 78** (normal range 80-99)
  - **lymphocytes 9.39** (normal range 1-4.00)

- Blood film compatible with glandular fever
- Glandular fever screen positive
• Ferritin 109
• **Iron 4** (normal range 11-31)
  Transferrin 3.0
  **Iron saturation 5** (normal range 15-55)

• **GGT 94** (normal range 0-73)
• Bilirubin 14
  **ALP 208** (30-130 – improving)
  **ALT 201** (improving)
  Albumin 46
• **CRP 43** (normal range 0-10)
• Glucose 5.3
• Clotting screen normal
• Electrolytes normal
• **Alpha-1 antitrypsin 2.52** (slightly raised)

• CMV/Hepatitis A/Hepatitis B/C screen negative
Glandular fever

- Clinical syndrome comprising fever, pharyngitis and lymphadenopathy associated with atypical lymphocytosis

- Incubation period 4-8 weeks

- 90% of cases caused by acute EBV infection

- Other important causes include CMV, toxoplasmosis and HIV infection

- Heterophile antibody tests are used to confirm that glandular fever is due to acute EBV infection
• Heterophile antibodies are a group of IgM antibodies induced by acute EBV infection that react to red blood cell antigens from other species

• These include the Monospot or Paul-Bunnell test

• Heterophile antibodies are present at clinically significant levels by time of symptom onset and **peak between 2 and 5 weeks later**

• Identifiable levels may persist for up to 1 year in a patient with glandular fever
• The presence of heterophile antibodies in a symptomatic adolescent or young adult has a sensitivity of approximately 90% and specificity of almost 100% for glandular fever.

• However, false negatives do occur in 25% of people early in the course of their illness (e.g. the first week).

• **LFTs are abnormal in more than 80% of people with glandular fever** but acute liver failure associated with EBV is very rare.

• Normal LFTs do not exclude glandular fever.
• Any further tests you would consider in this patient?
• Is there a possibility of Coeliac disease?

• Coeliac disease can be a cause of iron deficiency as well as abnormal LFT.. So yes!
Coeliac disease

- Coeliac disease may affect the liver and also be associated with autoimmune hepatitis

- Coeliac disease is diagnosed in as many as 9% of patients with cryptogenic hypertransaminasaemia

- A mild elevation in ALT and/or AST is common in untreated Coeliac Disease, occurring in 40% of adults and 50% of children with Coeliac disease.
- LFTs normalise within 1 year of a gluten-free diet in 95% of patients.

- Lack of normalisation of LFTs at 12 months in a Coeliac patient on a gluten free diet would suggest coexisting liver disease.
General principles when investigating/interpreting LFTs

• Always repeat any abnormal test in the first instance

• Remember normal LFTs **do not** exclude liver disease and some patients can have severe liver disease with only slightly abnormal liver enzymes

• Interpret LFTs in a clinical context

• Take a careful history for risk factors, drugs, alcohol, comorbidities and autoimmunity

• Perform a physical examination to look for evidence of liver disease
• If mild abnormalities and no risk factors for serious liver disease repeat after an interval

• Look at the pattern of abnormality

• Look at magnitude of abnormality

• Look at rate of change in LFTs

• Look at the nature of the course of abnormalities – fluctuating vs progressive
Abnormalities

- **Isolated:**
  
  - Raised bilirubin
  - Raised ALP
  - Raised ALT
  - Raised GGT

- **Mixed:**
  
  - Cholestatic (ALP > ALT)
  - Hepatitic (ALT > ALP)
Raised bilirubin

- Slightly raised isolated levels are common and usually not clinically significant
- Conjugated vs unconjugated
Raised bilirubin

- Diseases that increase the rate of bilirubin formation such as haemolysis or diseases that reduce the rate of conjugation such as Gilberts syndrome, produce an **unconjugated hyperbilirubinaemia**

- Diseases that reduce the rate of secretion of conjugated bilirubin into the bile or flow of bile into the intestine produce a mixed or predominantly **conjugated hyperbilirubinaemia**. Elevated conjugated bilirubin levels usually indicate hepato-biliary disease
Raised bilirubin

• Is this haemolysis?
  Haemolysis screen – Haptoglobins (reduced in haemolysis), reticulocytes (increased in haemolysis), Coomb’s test
  FBC, Blood film

• If only abnormal bilirubin then consider drugs or Gilbert’s syndrome as most common causes.
Raised ALP

- Two main sources are **liver** and **bone**

- **Physiological causes:**
  
  3\(^{rd}\) trimester Pregnancy (produced by placenta)
  Adolescents (increased bone turnover)
  Bone growth
Raised ALP

- **Pathological causes:**
  - Bile duct obstruction
  - Primary biliary cirrhosis /cholangitis
  - Primary Sclerosing Cholangitis
  - Drug induced
  - Metastatic liver disease
  - Bone disease (e.g. Pagets, Osteomalacia, hyperparathyroidism, vitamin D deficiency, fractures)
Raised ALP

- GGT can be useful to **EXCLUDE** liver disease. Sensitive biomarker for hepato-biliary disease but poor specificity.

- If normal GGT then assume bony origin – can also request ALP Iso-enzymes to differentiate

- Ultrasound abdomen/liver to look for pathological causes

- If persistently raised ALP of liver origin
  ? Primary biliary cirrhosis – check anti-mitochondrial antibodies and immunoglobulins.
Primary biliary cirrhosis

- Autoimmune
- Predominantly women affected – usually middle-aged
- Symptoms and signs include fatigue, itching, xanthelasma
- Advanced disease can cause jaundice
- Disease is characterised by interlobular bile duct destruction
- Increased risk of developing osteoporosis and oesophageal varices
Primary biliary cirrhosis

- Poor lipid-dependent absorption of vitamins A, D, E and K. Supplementation needed if bilirubin raised

- Bilirubin levels have prognostic significance

- No cure but medication can slow progression and alleviate symptoms
Raised ALT

- ALT<120 IU/L considered mild
  ALT >120 IU/L generally considered severe

- Common causes
  Alcohol, viral hepatitis, medication e.g. Statins,
  Non-alcoholic fatty liver disease (NAFLD)

- Less common causes
  Autoimmune hepatitis, Wilson’s disease, Haemochromatosis,
  Alpha-1-antitrypsin deficiency
Raised ALT

- Non-hepatic causes (usually <120 IU/L)

Coeliac disease, strenuous exercise, muscle disease, endocrine disease (hypo/hyperthyroidism)
Second line tests to consider...

- Lipid profile
- AST
- GGT
- TSH
- Coeliac screen
- Ferritin and iron studies
- Glucose
- Clotting screen
- Ultrasound scan

- Liver autoantibodies (Antinuclear/Smooth muscle/Mitochondrial/Liver Kidney microsomal)
- Virology for Hepatitis B and C
- Alpha-1-antitrypsin assay
- Caeruloplasmin (<45 years)
- Immunoglobulins
Raised ALT

- [An ALT investigation pathway - West Suffolk CCG](http://www.penninegplearning.co.uk/disclaimer/)
- [Yorkshire and Humber Liver network investigating LFT guideline](http://www.penninegplearning.co.uk/disclaimer/)
NAFLD

- Now most common cause of chronic liver disease in developed countries. Prevalence estimated at 20-30% in general population.
- Caused by excess fat in liver that is not due to excessive alcohol consumption or other secondary causes such as medication, hepatitis C infection
- Patients usually have raised ALT with AST:ALT ratio <0.8. In advance disease (NASH) with fibrosis AST:ALT ratio >0.8. NASH prevalence estimated at 2-3%.
- In alcoholic fatty liver disease AST:ALT >1.5
NAFLD

• Ultrasound is first line investigation but may need liver biopsy if evidence of disease progression to fibrosis and/or cirrhosis

• Risk factors for NAFLD include:

  Obesity
  Type 2 diabetes
  Dyslipidaemia
  Metabolic syndrome
Management of NAFLD

- Weight loss
- Orlistat as an aid to weight loss
- Dietary changes – avoid saturated fats, simple carbohydrates and sweetened drinks
- Exercise – improves LFTs independent of weight loss
- Limit alcohol intake
- Statins for dyslipidaemia – Patients with NAFLD should continue to take them despite raised ALT. Only consider stopping if levels double in first 3 months of taking them.
Raised GGT

- Causes include:
  - Hepato-biliary disease
  - Pancreatic disease
  - Alcohol
  - Diabetes
  - Drugs including oral contraceptive pill
  - Non-alcoholic fatty liver disease
Albumin

- A sensitive marker of liver function, although it may not be useful in the acute stages as has a long half-life (20 days)

- Low levels can be due to nutritional problems, excess protein loss through renal disease or failure of protein synthesis through loss of functioning liver tissue and some inflammatory conditions where the liver switches to making other proteins
Prothrombin time

• Another sensitive marker of synthetic liver function

• Is more likely to be deranged quicker than albumin in acute liver failure
Ferritin

• An intracellular iron storage protein and a marker of iron stores

• Low ferritin values provide absolute evidence of iron deficiency

• Raised levels often indicate iron overload but are not specific, as ferritin is an acute phase protein and also released from damaged hepatocytes
Ferritin

Causes of raised ferritin **without** iron overload:

<table>
<thead>
<tr>
<th>Common</th>
<th>Liver disease e.g. Non-alcoholic steatohepatitis or viral hepatitis</th>
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<tbody>
<tr>
<td></td>
<td>Alcohol excess</td>
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<td>Acute and chronic inflammatory conditions</td>
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<td>Infections</td>
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<td>Malignancy</td>
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<td>Renal failure</td>
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<td>Metabolic syndrome</td>
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| Less common                   | Thyrotoxicosis, Acute myocardial infarction                        |
Ferritin

Causes of raised ferritin with iron overload:

Iron supplements, Iron infusions, Transfusions

Chronic anaemia or known haemoglobinopathies mainly due to regular transfusions

Porphyria cutanea tarda – a hepatic porphyria presenting with cutaneous sensitivity and liver dysfunction to hepatic iron deposition

Hereditary haemochromatosis
Ferritin

- Check serum transferrin saturation with raised ferritin to exclude iron overload as a cause

- Fasting sample as transferrin levels can temporarily rise with food ingestion

- If **transferrin saturation <45 % in female or <50 % in males** then look for reactive or secondary cause of raised ferritin – NOT iron overload

- If transferrin saturation >45 % confirms iron overload - consider screening for HFE mutation for hereditary haemochromatosis
Ferritin

- Unexplained ferritin levels >1000 µg/L warrant referral to hepatology for further investigation
Summary

• Always repeat any abnormal LFTs in first instance

• Look at the pattern of abnormality

• Take a full history and perform clinical examination and interpret in light of the clinical context

• Request follow-on tests depending on likely diagnoses

• If unsure, seek specialist advice!
References

- Lab Investigation of Glandular Fever bpac.org.nz
- Prevalence and causes of abnormal LFTs in patients with Coeliac Disease -medscape.com
- Yorkshire and Humber Liver Network Guidance on Investigating Abnormal LFTs
- West Suffolk CCG ALT pathway
- GP notebook NAFLD
• Newcastle management asymptomatic patients with abnormal LFTs guideline

• Derbyshire abnormal LFTs guideline

• Patient UK

• Interpreting raised serum ferritin levels BMJ practice August 2015