Cases in primary care laboratory medicine

Biochemical “liver function tests”

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This article considers two common scenarios of “abnormal” liver test results that may be seen in primary care. It looks at the pitfalls in liver testing and summarises guidance, including further investigations that may or may not be warranted

“Abnormal” liver results (bilirubin or enzymes produced by the liver) are a common finding in the investigation of patients presenting with non-acute illness and often raise questions about the need for, and timing of, further investigation. Although the management of overt liver disease will usually include referral to a secondary care specialist, the thresholds for referral and further investigation in clinically silent situations can be unclear.

Case 1

A 27 year old man presented to his general practitioner with a one week history of fever and malaise. On examination he appeared slightly jaundiced and was febrile (38.5°C). He had no evidence of pharyngitis, cervical lymphadenopathy, or organomegaly.

A full blood count was reported as haemoglobin 142 g/l, increased white cell count ($10.4 \times 10^9/l$), and a lymphocytosis ($5.1 \times 10^9/l$). Routine chemistry had been done at the same time and showed urea, creatinine, and electrolytes within laboratory reference ranges, raised bilirubin (42 $\mu\text{mol/l}$) with normal aspartate and alanine transaminases and alkaline phosphatase. A heterophilic antibody test for Epstein-Barr virus (monospot) was positive, and the patient was diagnosed as having infectious mononucleosis. Further testing showed that the bilirubin was 95% unconjugated, haptoglobins and lactate dehydrogenase were normal, no reticulocytes were present, and a blood film was normal in appearance with atypical lymphocytes present.

His symptoms were treated and when he was seen two weeks later his fever had resolved, he was clinically improved, and a repeat liver profile showed that his bilirubin had fallen but was still raised (28 $\mu\text{mol/l}$). After discussion with the local laboratory no further investigations were recommended and a presumptive diagnosis of Gilbert's syndrome was made. The patient made an uncomplicated recovery.

Case 2

A 43 year old man with type 2 diabetes was seen for annual review in a diabetes clinic. He had had diabetes for five years and was being managed with diet and metformin. His diabetes control had been good and recently glycosylated haemoglobin was 7.1%. He had been

Summary points

Most conventional “liver function tests” are not tests of liver function, and most results are not specific to the liver

Gilbert's syndrome is a common cause of isolated raised unconjugated bilirubin

Raised transaminases (> 2 times upper limit of normal) are commonly associated with biopsy proved liver disease and justify further testing

The commonest reason for raised transaminases is alcoholic or non-alcoholic fatty liver disease, but other causes should be considered

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receiving simvastatin 20 mg lipid lowering therapy for three years, and when he was seen his cholesterol was 4.8 mmol/l, triglycerides 2.1 mmol/l, and high density lipoprotein cholesterol 1.1 mmol/l. His declared long term alcohol consumption, unchanged recently, was about 15 units per week.

Liver enzymes showed alanine transaminase 186 IU/l (normal < 40 IU/l), normal alkaline phosphatase of 98 IU/l, bilirubin 21 $\mu\text{mol/l}$, albumin 42 g/l, total protein 84 g/l. Urea, creatinine, and electrolytes were within the laboratory reference ranges. Two years before, alanine transaminase had been 88 IU/l.

A repeat liver profile three months later showed that alanine transaminase was 202 IU/l, alkaline phosphatase 88 IU/l, bilirubin 23 $\mu\text{mol/l}$, albumin 44 g/l, total protein 84 g/l. Results of further investigations were: autoantibody screen (including anti-mitochondrial, antinuclear antibodies) negative, hepatitis viral serology negative, α_1 antitrypsin 1.2 g/l (normal range 0.8–2.0 g/l), ferritin 1080 mg/l (normal range 20–250 mg/l)

The patient was referred to secondary care for assessment. He proved to be homozygous for the C282Y mutation of the HFE gene, which is responsible for most genetic iron overload in the United Kingdom.

How should I investigate an isolated “slightly raised” bilirubin in an asymptomatic adult?

- Values up to 20% more than the upper limit of normal are likely to be statistically rather than clinically “abnormal”
- Values < 1.5 times the upper limit of normal—interval retest in 1–3 months unless clinical suspicion of disease
- Values > 1.5 the upper limit of normal—confirm proportion of indirect (unconjugated) bilirubin
- If > 70% of bilirubin is unconjugated, the diagnosis is probably Gilbert’s syndrome: no further testing is needed if disease is non-progressive on interval retesting, unless haemolysis is suspected. If unconjugated bilirubin is rising on retesting, consider haemolysis and test haptoglobin, lactate dehydrogenase, and blood count with reticulocyte count
- Values > 3 times the upper limit of normal—clinical disease is likely and further investigation is required. Consider ultrasound (if > 50% of bilirubin is conjugated) or haemolysis (if > 70% is unconjugated)

A liver biopsy confirmed the clinical diagnosis of haemochromatosis with severe hepatic fibrosis.

Discussion

The changes found on liver profiles can occur for reasons other than altered liver function. Incidental rises in bilirubin or in one or more “liver” enzymes are commonly found in everyday practice, and it may be difficult to determine the threshold for further investigation.

Case 1

Epstein-Barr virus infection (infectious mononucleosis) may produce changes in liver profiles in various ways. It may present with appearances of hepatitis, characterised by rises in transaminases, reflecting hepatocellular damage, particularly in postadolescent patients.¹ It may be associated with haemolysis, which is normally autoimmune in origin, and is associated with a rise in unconjugated bilirubin due to haem breakdown, a fall in serum haptoglobins, a rise in lactate dehydrogenase, reticulocytosis, and characteristic blood film appearances.

Viral illness is also a common trigger, producing a rise in unconjugated bilirubin in patients with Gilbert’s syndrome, a congenital defect of intrahepatic conjugation of bilirubin with glucuronic acid which seems to

be of little clinical or prognostic importance. The defect may be present in up to 6% of white populations (varying in other racial groups) and is typically associated with rises in serum unconjugated bilirubin not exceeding 68–85 $\mu\text{mol/l}$, depending on the study.^{2–3}

Although Gilbert’s disease can be diagnosed by subjecting patients to a 48 hour fast, the diagnosis is typically made after excluding other causes of raised unconjugated bilirubin.^{3–4} Liver disease is unlikely in the presence of raised unconjugated bilirubin in adults, as most obstructive or hepatic processes result in a rise in conjugated (indirect) bilirubin or in a mixed picture of abnormal results on liver tests. When patients with alcohol induced changes are excluded, the commonest biopsy findings in patients with transaminases more than twice the upper limit of normal is non-alcoholic fatty liver disease.

Case 2

Raised transaminases in a diabetic patient are often produced by non-alcoholic fatty liver disease associated with fat deposition secondary to hypertriglyceridaemia and insulin resistance. Transaminases are a poor reflection of underlying liver disease, but raised transaminases (more than twice the upper limit of normal) are often associated with biopsy proved disease.⁵ In the era of widespread prescribing of statins, these drugs are often blamed for increases in transaminases, but randomised trials have not shown this to be a common effect and in the large heart protection study transaminases more than three times the upper limit of normal were not more common in patients treated with statins.⁶

Diabetes mellitus is a presenting feature of haemochromatosis in about 20% of patients, but may also coexist. A raised ferritin concentration is also commonly seen in non-alcoholic fatty liver disease or with chronic alcohol excess, where it is probably due to hepatic injury rather than true iron overload, although a mild increase in hepatic iron stores may occur. Haemochromatosis, however, is a rare cause of diabetes.⁷ Recommendations for the investigations of isolated “raised liver function tests” are shown in the boxes.

What are the sources of evidence?

A review of best practice in primary care pathology published in the *Journal of Clinical Pathology* indicates the varying degrees of evidence that back up these recommendations.⁸ Evidence for further investigation

Investigations in asymptomatic patients with raised liver enzymes⁹

Test	Abnormality	Interpretation
Suggested first investigation		
Full blood count	Macrocytosis Thrombocytopenia	Suggests alcohol excess if γ glutamyl transferase also raised Possible hypersplenism (portal hypertension)
Autoantibodies	AMA positive, IgM ASM or ANA positive, IgG	Probable primary biliary cirrhosis Strongly suggestive of autoimmune hepatitis
Ferritin	Raised	Possible haemochromatosis, seek advice if raised
Hepatitis B surface antigen	Positive	Chronic infection probable
Hepatitis C antibody	Positive	Chronic infection possible
If no diagnosis obtained		
Liver ultrasound	Mass or dilated ducts	Tumour/stones
Anti-endomysial antibodies	Positive	Suggests coeliac disease
α 1 antitrypsin concentration	Low	Suggests deficiency; phenotype required (possible PIZZ)
Others (eg, caeruloplasmin, urine copper) as dictated by clinical context	Low	Wilson’s disease

Fatty liver disease is a common cause of raised transaminase levels

when results of liver tests are out of the normal range is based mostly on observational studies of investigation of patients whose test results have been abnormal and the subsequent findings on liver biopsy. The thresholds that trigger further investigation seem to be based on logistics and availability of resources. Apart from those caused by alcohol, the great majority of transaminase abnormalities are found to be related to non-alcoholic fatty liver disease. No drug treatment for this disorder has been proved, but exercise and weight loss improve results of liver function tests. The principle of investigating these patients seems to be

How should I investigate abnormal transaminases in asymptomatic patients without risk factors for, or clinical features of, liver disease?

- If raised and $<3 \times$ upper limit of normal—recheck in 1–3 months
- If still raised (two measurements, six months apart)—further investigation indicated as shown in other box
- If more than three times upper limit of normal (single measurement), further investigation indicated as shown in the table

How should I investigate abnormal transaminases in patients with risk factors for, or clinical features of, liver disease?

- Further investigations are advised for any enzyme rise associated with risk factors for, or clinical evidence of, liver disease except where an apparent cause is found (hypertriglyceridaemia, diabetes, alcohol, overweight), for which a six month trial of appropriate intervention is recommended

based mainly on detecting potentially treatable causes, as in case 2 above, and on the theoretical assumption that identifying non-alcoholic fatty liver disease will improve the prognosis of the patients concerned and allow treatment in the future.

The principle of interval retesting to distinguish one-off results from stable and progressive increases seems sound. There is guidance, but limited evidence, on retesting interval.⁸ In patients without symptoms, and in view of the slow time course of the potential underlying diseases, retesting with an interval of months rather than weeks seems reasonable when rises are “minor” (up to 3–5 times the upper limit of normal). What is “normal” varies by ethnic origin and age; this confusion could be solved by establishing reference ranges specific for particular groups. The term “normal range” introduces further confusion, as the values reflect a statistical range and not a definition of what is not pathological. Results outside of these ranges therefore do not necessarily indicate disease.

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The first teaching ward round: Leyden 1660

I us[ed] a method not hitherto in use . . . took them daily into the public hospital [to] see the sick to whose complaints and other notable symptoms I directed attention, asking immediately afterwards what they had observed in the disorders of the patient; their views as to the causes and proper treatment, and their reasons for the same. With me they confirmed the happy results of the treatment, . . . or assisted in the examination of the cadavers.

Franciscus Sylvius. *Epistola Apologetica* 1664. Cited by Baker F. The two Sylviuses, an historical study. *Johns Hopkins Hosp Bull* 1909;20:329–39

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