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FIFTEEN-MINUTE CONSULTATION: WHEN TO SUSPECT LIVER DISEASE

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Key words: Liver function test; paediatric; NAFLD; biliary atresia; acute liver failure
ABSTRACT

Liver disease have protean presentations: acute liver failure, insidious chronic liver disease, or an incidental finding of abnormal liver function tests. In this article we discuss the identification of liver disease and ‘red flags’ in four specific clinical situations: conjugated prolonged jaundice; acute liver failure; new-onset jaundice in a teenager; and incidental finding of abnormal aminotransferases. These scenarios are used to illustrate how ancillary investigations aid diagnosis.
INTRODUCTION

Liver disease in children has varied presentation, ranging from the frequently encountered prolonged, neonatal jaundice to the comparatively rare acute liver failure. Due to the supra-regional specialisation of UK hepatology services, many paediatricians may not have extensive clinical exposure to these conditions. This article will focus on how blood tests may be interpreted in clinical context to identify important liver pathologies.

Liver function tests (LFTs) are among the most frequently performed blood tests in children. They are often requested as part of an automated biochemistry panel, which results in incidental identification of abnormalities. Whilst they may be valuable first-line investigations in the assessment of liver disease, they usually do not test the functional capacity of the liver, nor are abnormalities necessarily specific for individual liver diseases, though some patterns may be observed.

Due to the liver's considerable functional reserve, liver disease often remains subclinical until relatively advanced[1,2]. Therefore, in addition to patients with symptoms or signs of liver disease (e.g. jaundice, splenomegaly), evidence of liver (dys)function should be actively sought in certain groups of patients, including: hepatotoxic medication (e.g. methotrexate) and systemic conditions that may affect the liver (e.g. ulcerative colitis with associated sclerosing cholangitis, or obesity and NAFLD).

BACKGROUND PATHOPHYSIOLOGY

Appropriate requesting and interpretation of liver function tests requires an understanding of hepatobiliary cellular structure, liver physiology, and non-liver sources of certain enzymes or proteins measured by LFTs.

Liver microanatomy and physiology

The functional unit of the liver is the hepatocyte. Plates of hepatocytes comprise the hepatic lobule, with portal tracts at the periphery and a central vein in the middle (see figure 1). Arterial and portal venous blood mixes in sinusoids that run either side of plates of hepatocytes. Hepatocytes secrete products for excretion into bile in canaliculi (formed from the lateral wall of hepatocytes), which drains into bile ducts. Cholangiocytes (biliary epithelial cells) line bile ducts and the remainder of the biliary system.
There are several key functions of the liver, including synthetic, metabolic, production of bile, and detoxification. Though variable, end-stage chronic liver disease tends to manifest in blood tests as coagulopathy and hypoalbuminaemia, whilst acute liver failure results in coagulopathy, hypoglycaemia, and hyperbilirubinaemia. The degree of abnormality of INR, albumin, pH, lactate, bilirubin, and glucose does correlate with the degree of hepatic dysfunction.

**Bilirubin**

Bilirubin is the breakdown product of haem, 95% of which comes from red cell haemoglobin. It is produced as unconjugated bilirubin by the reticuloendothelial system and transported to hepatocytes, where it is converted to conjugated bilirubin before being exported into canaliculi (see figure 2).
Serum bilirubin may be measured in total, or split into conjugated and total forms. Measurement of direct bilirubin is assumed to be synonymous with conjugated bilirubin, however there is a small amount of unconjugated bilirubin unbound to albumin (‘free’), which will also react (see figure 3). The greater the total bilirubin, the more free unconjugated bilirubin will be present. Therefore, the higher the total bilirubin, the more the direct bilirubin will be influenced by unconjugated bilirubin[3].

<Figure 3>

Liver enzymes
The enzymes that comprise the typical biochemical panel of LFT are not only expressed in the liver (see table 1). Hence, AST/ALT elevation could be of muscle origin and concomitant CK measurement is usually helpful to attribute the aminotransferase rise to muscle disease[3]. Mild elevations of ALT and AST occur in almost any liver condition, however, the degree of increase in aminotransferases does not give useful information about liver function or underlying diagnosis.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Source</th>
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| Aminotransferases | AST - Liver, heart, skeletal muscle, kidney, pancreas, red cells  
|              | ALT – Liver, skeletal muscle, heart         |
| ALP         | Bone, small intestine, liver, placenta, kidney |
| GGT         | Biliary epithelial, hepatocytes, renal tubules, pancreas, brain, breast, small intestine |

Table 1. Sources of hepatic enzymes.
<Table 1>
Typically, ALP and GGT both rise in response to biliary injury (intra- or extra-hepatic), however ALP correlates with bone turnover in children, therefore GGT is used in preference as the main biliary enzyme during childhood. However, both normal and elevated GGT levels may be of diagnostic significance, as discussed below, particularly in differentiating intrahepatic cholestasis syndromes.

Liver ‘function’ tests
Hepatocytes synthesise the majority of all serum proteins, including albumin and clotting factors. Albumin is used as a medium-term marker of hepatic synthetic function[4] whilst INR (international normalised ratio) and PT (prothrombin time) can be used as short-term markers of synthetic capacity, if haematological causes and vitamin K deficiency have been ruled out. It should be remembered that INR was designed for monitoring of warfarin activity however is a useful method for standardising prothrombin time between laboratories.

Encephalopathy results from the accumulation of nitrogenous compounds and endogenous opioids, therefore elevation of ammonia is used in the diagnosis of hepatic encephalopathy. It has a good negative predictive value: hepatic encephalopathy is unlikely in the setting of a normal ammonia[5]. Urea cycle disorders should also be considered when ammonia level is elevated.

CASE 1:
A 6 week old infant is referred to the paediatric unit due to prolonged jaundice. She has pigmented stools, colour confirmed by the treating physician. Blood results: total bilirubin 168 µmol/L, conjugated bilirubin 140 µmol/L, ALT 150 IU/L, AST 161 IU/L, GGT 30 IU/L, Alb 36 g/L, INR 1.2.

Prolonged, conjugated jaundice
Prolonged jaundice is defined as visible jaundice at 14 days in term infants or 21 days in those born at less than 37 weeks. The most common cause for unconjugated hyperbilirubinaemia is breastfeeding associated jaundice, which may be present in 25-45% of breastfed neonates[6]. Whereas, there is a wide differential for conjugated hyperbilirubinaemia (where conjugated bilirubin comprises >20% of the total bilirubin or an absolute value of 25 µmol/L[7,8], see table 2) as the neonatal liver has a tendency to develop cholestasis in response to a variety of insults. Initial investigation should focus on: confirming conjugated hyperbilirubinaemia, looking for evidence of acute liver failure or sepsis, and then investigating the cause (table 2)[8]. Early discussion with a hepatology unit facilitates rapid investigation of time-critical diagnoses.

<table>
<thead>
<tr>
<th>Test</th>
<th>Abnormality</th>
<th>Suggests a diagnosis of</th>
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<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
**Viral hepatitis serology**
Positive results on serology
HSV, hepatitis A/B/C viruses

**Congenital infection serology**
Positive IgM CMV PCR (urine & blood)
Toxoplasma, rubella, CMV, HSV

**Blood & urine culture**
Bacterial growth
Sepsis

**Immunoreactive trypsinogen (IRT) – under 2-3 weeks age**
Raised IRT
Cystic fibrosis

**Sweat test**
Raised sweat chloride

**Alpha-1-antitrypsin levels and Pi type**
PiZZ
Alpha-1-antitrypsin deficiency

**Galactose-1-phosphate uridyl transferase**
Low enzymatic activity
Galactosaemia

**Thyroid function tests**
Low T4, high TSH
Congenital hypothyroidism

**Plasma amino acids**
Raised tyrosine
Tyrosinaemia
Non specific

**Urine organic acids**
Raised succinylacetone
Tyrosinaemia

**Alpha fetoprotein**
Significantly increased*
Hepatoblastoma, tyrosinaemia, or non-specific

**Ultrasound abdomen**
Absent or abnormal gall bladder
Biliary atresia
Cyst of common bile duct
Choleodochal cyst

| Table 2. Initial investigations used in identifying causes of neonatal conjugated hyperbilirubinaemia. *Elevated alpha fetoprotein in neonates may be normal. CMV – cytomegalovirus; EBV – Epstein-Barr virus; HSV – herpes simplex virus; IRT – immunoreactive trypsin; PCR – polymerase chain reaction; TSH – thyroid-stimulating hormone |

Differential of conjugated hyperbilirubinaemia
Biliary atresia is an important cause of neonatal cholestasis, accounting for 25% of all neonatal conjugated hyperbilirubinaemia presenting to a tertiary centre, and early treatment significantly improves outcomes[9]. It typically presents with pale stools (not golden yellow or green; any other colour is compatible with diagnosis of biliary atresia), conjugated hyperbilirubinaemia, aminotransferases in the hundreds, and an elevated GGT. Physical inspection of the stool to confirm the pigment by healthcare professionals is strongly recommended.

The infant in this vignette has a conjugated hyperbilirubinaemia but her stools are pigmented and she has a low GGT. She is not in liver failure (and does not have vitamin K deficiency) given her normal INR. The pigmented nature of her
stools does not exclude cholestasis. However, the low GGT helps to narrow the differential diagnosis by favouring progressive familial intrahepatic cholestasis (PFIC). This infant will need referral to a liver centre for further management.

PFIC is a group of rare conditions caused by germline mutation of canalicular membrane transporters. PFIC type 1 may be associated with short stature, short digits, and diarrhoea. Bile Salt Export Protein (BSEP) deficiency (PFIC type 2) has no additional extra-hepatic phenotype. Though variable, the natural history of low GGT intrahepatic cholestasis is unremitting progression with end-stage liver in early childhood

**CASE 2:**
A 5 year old presents to A&E with sudden onset jaundice and malaise. Blood results: total bilirubin 190 μmol/L, conjugated bilirubin 170 μmol/L, ALT 850 IU/L, AST 800 IU/L, GGT 110 IU/L, Alb 35 g/L, INR 3.1. Repeat INR 4-hours after 2mg IV vitamin K is 3.0.

**Acute liver failure**
This girl has presented with acute liver failure (ALF), as identified by coagulopathy (INR >2.0) that is unresponsive to vitamin K associated with biochemical evidence of hepatocellular injury. An INR >1.5 with evidence of encephalopathy would also be classed as ALF. This is a medical emergency; any child with an abnormal INR and suspected ALF should be referred to a hepatology transplant unit urgently. The differential diagnosis of ALF includes: infectious causes, metabolic causes, drugs & toxins (paracetamol overdose), rarities, and indeterminate (non-A-E hepatitis). Initial investigations are listed in table 3[10].

<table>
<thead>
<tr>
<th>Test</th>
<th>Abnormality</th>
<th>Suggests a diagnosis of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral hepatitis serology</td>
<td>IgM serology positive</td>
<td>Hepatitis A,B, &amp; E, CMV, EBV, adenovirus, enterovirus</td>
</tr>
<tr>
<td>Serum caeruloplasmin</td>
<td>Low levels</td>
<td></td>
</tr>
<tr>
<td>Serum copper</td>
<td>Elevated</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin and reticulocytes</td>
<td>Normocytic anaemia and raised reticulocytes</td>
<td>Wilson disease</td>
</tr>
<tr>
<td>Direct Coombs' test</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Urinary copper (pre-/post- penicillamine challenge)</td>
<td>Elevated urinary copper</td>
<td></td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>Positive ANA / ASMA / LKM / SLA / LC1</td>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>Increased IgG</td>
<td></td>
</tr>
</tbody>
</table>
Toxicology screen | Raised paracetamol level | Paracetamol overdose
---|---|---
Blood gas, serum amino acids, urinary organic acids, lactate, acyl carnitines, ammonia, mitochondrial DNA | Significant abnormalities | Metabolic diseases, including: mitochondrial, fatty acid oxidation defects, organic acidaemias, urea cycle defects

| Table 3 | Examples of initial blood investigations used in identifying the cause of acute liver failure. ASMA – anti-smooth muscle antibody; ANA – antinuclear antibody; EBV – Esptein-Barr virus; LKM – anti-liver-kidney microsomal antibodies; SLA – soluble liver antigen; LC1 – Liver cytosol 1 antigen. |

If there is no history of drug or toxin exposure, then the most likely causes are viral or metabolic. Viral causes include hepatitis A & E viruses (usually with history of travel to Asia or Africa). Cytomegalovirus, Epstein-Barr virus, and herpes simplex virus can cause ALF in immunocompromised patients.

Acute liver failure in infancy is more frequently due to metabolic disorders, including galactosaemia and tyrosinaemia. However, at 5 years old, Wilson disease may present acutely with Coombs’ negative haemolysis, acute liver failure, and renal impairment.

**Prognostic markers in ALF**

Early identification of children who will not survive with their native liver allows more rapid listing for transplant. The prognostic markers for poor outcome with ALF secondary to paracetamol overdose are different to those for ALF due to other causes. In non-paracetamol ALF an INR >4 alone would be a poor prognostic marker, whereas in paracetamol-induced ALF, acidosis, renal impairment, raised lactate, and encephalopathy are more important. There is no correlation between ALT and outcome in all cases of ALF.

**CASE 3:**

A 13 year old girl presents with jaundice after generally feeling unwell for 1 month. Blood results: total bilirubin 96 µmol/L, conjugated bilirubin 80 µmol/L, ALT 300 IU/L, AST 290 IU/L, GGT 106 IU/L, Alb 18 g/L, total protein 40 g/L, INR 2.5, platelets 113x10⁹/L. 4 hours after 10mg IV phytomenadione, INR 1.1. Urinary copper 0.4 µmol/24-hours, serum caeruloplasmin 0.5 g/L.

**Acute hepatic dysfunction, without liver failure**
This teenager has presented with a short history of new-onset conjugated jaundice associated with elevated aminotransferases. She is not in acute liver failure as her INR normalised following vitamin K administration, suggesting vitamin K deficiency, which may be due to inadequate bile acid delivery to the gut. This is an acute-on-chronic presentation, as evidence by low albumin, and thrombocytopenia due to hypersplenism from portal hypertension.

The main differential diagnosis is between autoimmune hepatitis and Wilson disease. The initial investigations above point towards autoimmune hepatitis due to low albumin and elevated immunoglobulins. Infection should also be considered as a cause for raised IgG. The normal caeruloplasmin and 24-hour urinary copper make Wilson disease unlikely.

**Autoimmune hepatitis**

Autoimmune hepatitis (AIH) is a rare condition of hepatic inflammation associated with circulating non-organ specific autoantibodies[11]. It demonstrates a good response to immunosuppression, which greatly improves the clinical outcome for affected children. There are three types of AIH, based upon the autoantibodies present (see table 4), though they have a similar clinical course.

The two most discriminatory laboratory investigations are immunoglobulin G (IgG) titre and high-titre non-organ-specific autoantibodies[11]. IgG is raised in 85-90% of all patients with AIH.

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibodies</td>
<td>Anti-SMA, ANA, pANCA</td>
<td>Anti-LKM1 /-LC1</td>
</tr>
<tr>
<td>Age</td>
<td>Peak at 10-20 and 45-70 years</td>
<td>2-14 years</td>
</tr>
<tr>
<td>Increased IgG</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Associations</td>
<td>HLA B8, DR3, DR4</td>
<td>HLA DR7, DR3</td>
</tr>
</tbody>
</table>

*Table 4. Differences of type 1, 2, and 3 autoimmune hepatitis[12]. SMA – smooth muscle antibody; ANA – antinuclear antibody; LC1 – liver cytosol 1; LKM – Liver-kidney microsomal antigen; LP – liver-pancreas; pANCA – perinuclear antineutrophil cytoplasmic antibodies; SLA – soluble liver antigens*
Other features needed to exclude an alternative diagnosis are a negative viral hepatitis screen and exclusion of Wilson disease (WD). Ruling out WD is challenging, though patients with WD may have higher bilirubin, ALT/AST in low hundreds, and low ALP. Caeruloplasmin is low in the majority of affected patients. It is not 100% sensitive (see table 5) [13] but it is the authors’ clinical experience that most patients have caeruloplasmin <0.05g/L. Urinary copper should be high (with further elevation after penicillamine) but definitive diagnosis of WD needs genetics (for ATP7B mutation) or liver copper measurement.

<table>
<thead>
<tr>
<th>Caeruloplasmin concentration cut-off (g/L)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.20</td>
<td>98</td>
<td>56</td>
<td>48</td>
<td>99</td>
</tr>
<tr>
<td>0.14</td>
<td>93</td>
<td>100</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>0.10</td>
<td>79</td>
<td>100</td>
<td>100</td>
<td>92</td>
</tr>
</tbody>
</table>

Table 5[13]. Data on the validity of use of 3 different cut-off thresholds of caeruloplasmin for diagnosis of Wilson disease in patients clinically suspected of having the condition.

Patients with features suggestive of AIH should be referred to a tertiary liver centre, where a liver biopsy may be performed to confirm the diagnosis prior to starting treatment.

------------------------------------------------------------------------------------------------------

**BOX 2. ‘Dos and Don’ts’ in suspected liver disease**

**Dos**
- Check the prothrombin time (or INR)
- Discuss early with a hepatology centre
- Closely monitor liver function tests while awaiting a formal plan of management

**Don’ts**
- Use ALT or AST as a marker of hepatic function or severity of disease
- Ignore unexplained abnormal LFTs, even in clinically well children
- Assume a diagnosis without completing investigations (e.g. diagnosing NAFLD without fully excluding Wilson disease)
CASE 4:
A 15 year old is seen by the paediatric surgical team with vague abdominal pain. BMI 32.9 kg/m², BMI z-score +2.29, waist circumference 99th centile. Blood results: total bilirubin 13 µmol/L, ALT 110 IU/L, AST 101 IU/L, GGT 65 IU/L, Alb 35 g/L, INR 1.0.

Non-alcoholic fatty liver disease
This 15 year old has had incidental abnormalities LFT identified for which the most likely diagnosis is non-alcoholic fatty liver disease (NAFLD).

A careful history and examination should be undertaken for features of AIH, Wilson disease, and inborn errors of metabolism, as discussed above. An ultrasound demonstrating increased hepatic echogenicity (suggestive of fat infiltration), with a negative panel of secondary investigations (see table 6), and no history of alcohol intake would suggest a diagnosis of NAFLD in the context of an obese child, but specialist opinion is advised. Diagnosis can only formally be made by liver biopsy, which is also useful for staging disease.

<table>
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<td>Low levels</td>
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</tr>
<tr>
<td>Urinary copper</td>
<td>Elevated 24-hour excretion</td>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>Positive ANA / ASMA / LKM / SLA / LC1</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>Increased IgG</td>
<td></td>
</tr>
<tr>
<td>Alpha-1-antitrypsin levels and Pi type</td>
<td>PiZZ</td>
<td>Alpha-1-antitrypsin deficiency</td>
</tr>
<tr>
<td>Oral glucose tolerance test</td>
<td>Raised fasting insulin, or impaired glucose tolerance</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>High-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG)</td>
<td>Low HDL, high LDL, high TG</td>
<td>Dyslipidaemia or lysosomal acid lipase disease</td>
</tr>
</tbody>
</table>

Table 6. Ancillary investigations used in excluding secondary causes of hepatic steatosis and to look for end-organ damage in NAFLD. ASMA – anti-smooth muscle antibody; ANA – antinuclear antibody; CMV – cytomegalovirus; EBV –
Esptein-Barr virus; LKM – anti-liver-kidney microsomal antibodies; SLA – soluble liver antigen; LC1 – Liver cytosol 1 antigen.

Non-alcoholic fatty liver disease (NAFLD) describes a spectrum from isolated hepatic steatosis through non-alcoholic steatohepatitis (NASH) to fibrosis, ultimately leading to cirrhosis[14]. The condition is intimately related to obesity, insulin resistance, and the metabolic syndrome. Approximately 40% of obese children are affected with NAFLD[15]. Up to 9% of children with only ‘mildly’ abnormal LFT can have stage 3/4 fibrosis on biopsy[16] and 25% of those with stage 3/4 fibrosis have normal AST/ALT. There is no correlation between ALT and fibrosis; and fibrosis is the best marker of long-term outcome in adults[17]. This statement is true for many chronic liver diseases: normal AST and ALT give little information about progression of the condition.

**Management of NAFLD**

Long-term, patients with NAFLD are at increased risk of all complications of the metabolic syndrome, therefore children should be managed in accordance with guidance from the RCPCH Obesity Services for Children and Adolescents group[18].

There are no uniformly accepted pharmacological therapies recommended for paediatric NAFLD other than weight loss and exercise. Some suggested situations for when to refer to tertiary hepatology services are listed in Box 1[19].

**BOX 3. When to refer children with suspected non-alcoholic fatty liver disease**

- Diagnostic uncertainty
- Non-obese
- ALT or AST >1.5x upper limit of normal
- Splenomegaly
- Under 8 years of age
- Evidence of hepatocellular dysfunction or portal hypertension
- Persistently raised aminotransferases or gamma glutamyl transferase despite 3 months of lifestyle modification

**BOX 1. ‘Red flags’ in suspected liver disease**

- Any encephalopathy
- INR >1.5, which does not normalise with IV vitamin K
- pH <7.3
- Hypoglycaemia
- High or rising lactate
- High or rising creatinine or other evidence of renal dysfunction
- Evidence of hepatocellular dysfunction (low albumin, hypoglycaemia)
- Evidence of portal hypertension (splenomegaly, thrombocytopenia)

CONCLUSIONS
ALT/AST, bilirubin, and GGT should be thought of as a screen for acute hepatobiliary injury, though may be normal despite chronic liver disease. Whereas coagulation, glucose, albumin, and pH are more informative of physiological capacity. Diagnosis of specific pathologies requires an additional set of investigations with correlation to the clinical signs and symptoms of the patient.

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REFERENCES


FIGURE LEGENDS

**Figure 1.** Six portal triads are arranged around a central vein in the classical hepatic lobule. A hepatic acinus illustrates the direction of blood flow. The zoomed image shows plates of hepatocytes lining a sinusoid. Bile drains in canaliculi in the opposite direction to blood flow, back towards the portal triad.

**Figure 2.** Measurement of direct conjugated and total bilirubin. Sodium benzoate is added to free bound unconjugated bilirubin in measurement of total bilirubin. Direct bilirubin predominantly reflects conjugated bilirubin however a proportion of unconjugated bilirubin is unbound, which will influence the result.

**Figure 2.** Bilirubin metabolism with the site pre-, intra-, and post-hepatic jaundice illustrated.