INTRODUCTION OF LIVER FUNCTION TESTS PART 2

Compiled by Dr S. Mahabeer 1st Quarter 2017

Alkaline phosphatase (Alk phos)
This enzyme may be derived from liver, bone, intestine, kidneys and placenta. Physiological increases occur in children, adolescents, older women and those in the third trimester in pregnancy. In some individuals with blood type O or B, there may be an influx of intestinal Alk phos after eating a fatty meal.

The first step in the evaluation of the asymptomatic patient with elevated Alk phos levels where a physiological reason has been excluded, is to identify the source. GGT levels are usually elevated in parallel with Alk phos in patients with liver disorders, but are not increased in patients with bone disorders. Hepatic Alk phos levels rise due to increased synthesis and release of bile into the circulation. Due to the long half-life of Alk phos (approximately 1 week), it may take several days for Alk phos levels to normalise after resolution of biliary obstruction. Imaging of the liver by ultrasound is recommended if the raised Alk phos is found to be of liver origin. In certain cases a liver biopsy may be needed to obtain a final diagnosis.

A. Commoner causes of a marked elevation (more than 4 times the upper limit of normal) of Alk phos include:

<table>
<thead>
<tr>
<th>EXTRAHEPATIC BILIARY OBSTRUCTION</th>
<th>INTRAHEPATIC CHOLESTASIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholelithiasis e.g. acute cholangitis, biliary pancreatitis</td>
<td>Auto-immune cholestatic liver disease, e.g. primary biliary cholangitis, primary sclerosing cholangitis</td>
</tr>
<tr>
<td>Malignant obstruction e.g. pancreas, gallbladder, bile duct</td>
<td>Drugs and toxins associated with cholestasis</td>
</tr>
<tr>
<td>Biliary strictures</td>
<td>Infiltrative diseases e.g. sarcoidosis, lymphoma, amyloidosis, TB</td>
</tr>
<tr>
<td>Infections e.g. AIDS cholangiopathy, liver flukes, ascaris lumbricoides</td>
<td>Intrahepatic cholestasis of pregnancy</td>
</tr>
<tr>
<td></td>
<td>Metastatic carcinoma to the liver</td>
</tr>
</tbody>
</table>

B. Causes of a moderate elevation (less than 4 times the upper limit of normal) include:
- **Hepatic causes:** e.g. chronic viral and alcoholic hepatitis, cirrhosis, infiltrative diseases of the liver and hypo-perfusion states like sepsis and heart failure.
- **Non-hepatic causes:** conditions where there is high bone turnover e.g. hyperparathyroidism, hyperthyroidism, healing fractures, osteomalacia, Paget’s disease, osteogenic sarcoma and bone metastasis. Laboratory markers of high bone turnover that may assist diagnosis include bone-specific alkaline phosphatase, osteocalcin, hydroxyproline, and C-terminal crosslinks (CTX).
- **Extra hepatic diseases:** e.g. peritonitis, diabetes mellitus, myeloid metaplasia, and extra hepatic tumours like gastric, ovarian, uterine, lung, and Hodgkin’s lymphoma should be considered.

Gamma-glutamyltransferase (GGT)
GGT is found in hepatocytes and biliary epithelial cells, as well as in the pancreas, spleen, heart, brain, kidney and seminal vesicles. It is a sensitive indicator of hepato-biliary disease, but its usefulness is limited by its lack of specificity. Elevated levels are reported in pancreatic disease, myocardial infarction, renal failure, alcoholism, diabetes, chronic obstructive pulmonary disease, and in patients taking medications such as phenytoin, barbiturates and carbamazepine. GGT levels are physiologically increased in healthy full-term neonates (6 – 7 times the upper limit of normal of the adult reference range), and decreases over the first 5 – 7 months.

An elevated GGT in the absence of an increase in other liver biochemical markers should not lead to an exhaustive work-up for liver disease.

Bilirubin
Bilirubin is formed from the lysis of red blood cells in the reticuloendothelial system. Normally serum bilirubin is mainly in an unconjugated form, reflecting the balance between production and hepatobiliary excretion.

The initial step in the evaluation of an isolated hyperbilirubinaemia is to fractionate the bilirubin to determine whether it is a conjugated (direct) or unconjugated (indirect) hyperbilirubinaemia.
- An increase in conjugated bilirubin is due to decreased excretion into the bile ducts or leakage from hepatocytes into serum. An isolated increase in conjugated bilirubin is found in two rare, inherited conditions: Dubin–Johnson and Rotor syndromes. These should be suspected in patients with mild hyperbilirubinaemia, in the absence of other abnormalities of standard LFT. Both are benign conditions and typically present in the second decade of life.
- An increase in unconjugated bilirubin results from overproduction, impairment of uptake or impaired conjugation of bilirubin. In patients with increased unconjugated bilirubin, the development of jaundice during stress or fasting is consistent with Gilbert’s syndrome. Gilbert’s syndrome does not require any specific treatment and the patient can be reassured of the benign nature of this condition. Depending on the clinical scenario, evaluate the patient thereafter for haemolytic anaemia.
Liver synthetic function
Abnormal tests of synthetic function may occur in both hepatocellular injury and cholestasis. A low albumin suggests a chronic process, such as cirrhosis or cancer. A normal albumin suggests a more acute process, such as viral hepatitis. A prolonged prothrombin time (PTT) indicates either vitamin K deficiency due to prolonged jaundice and intestinal malabsorption of vitamin K, or significant hepatocellular dysfunction. The failure of the PTT to correct with parenteral administration of vitamin K suggests severe hepatocellular injury.

Isolated increase in Total Protein
When other elements of the LFT are normal with an increased total protein and normal albumin, then consider a diagnosis of hypergammaglobulinaemia. Protein electrophoresis will distinguish a polyclonal from a monoclonal increase.

SUMMARY
The initial evaluation of the patient with an abnormal LFT is a detailed clinical history to identify potential risk factors for liver disease, and a physical examination to look for clues to the aetiology, and the signs of chronic liver disease.

LFT abnormalities can be grouped into the following patterns: hepatocellular, cholestatic or isolated hyperbilirubinaemia. Patients with a hepatocellular process generally have a disproportionate elevation in AST and ALT compared with the Alk Phos and GGT, while those with a cholestatic process have the opposite findings. The serum bilirubin can be elevated in both conditions, and is not helpful in differentiating between them.

In patients with hepatocyte damage, ALT and AST are released from hepatocytes, leading to increased levels. The differential diagnosis is broad, and includes viral hepatitis, alcoholic liver disease, hepatic ischaemia, malignant infiltration and hepatotoxicity from drugs, toxins and some herbal preparations.

Cholestasis may develop in intra- or extra-hepatic biliary obstruction. The Alk Phos is typically increased to four or more times the upper limit of normal, with a parallel increase in GGT. Ultrasonography is useful to further characterise the cholestasis.

The evaluation of isolated bilirubinaemia begins with determining whether this is predominantly unconjugated or conjugated hyperbilirubinaemia.

REFERENCES
2. Friedman LS. Approach to the patient with abnormal liver biochemical and function tests. In UpToDate. Chopra S (Editor).
3. Larson AM. Drug induced liver injury. In UpToDate. Lindor KD (Editor).
4. Friedman LS. Liver biochemical tests that detect injury to hepatocytes. In UpToDate. Chopra S (Editor).