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Rationale and inconceivable liver function catechism

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ABSTRACT

Inconceivable liver function catechism are defined as increased levels of static biochemical tests, which include liver tests measured in serum - Aspartate Transaminase (AST), Alanine Transaminase (ALT), Alkaline phosphatase (ALP), bilirubin and measurements of biosynthetic liver function and International Normalized Ratio (INR), albumin. Common complaints include fatigue, malaise, nausea, hematemesis or melena/ haematochezia, pruritus, jaundice, easy bruising, anorexia, weight loss, abdominal swelling or right upper quadrant discomfort, confusion, and decreased libido or erectile dysfunction. The severity of the complaints is often related to the acuteness and severity of the liver injury. Even patients with advanced liver disease may remain asymptomatic, with normal or only mildly abnormal LFTs. Physical findings in patients with abnormal liver function catechism, Hepatomegaly or an unusually firm liver may be present. Jaundice, spider angiomata, palmar erythema, Terry nails, ascites, splenomegaly, dilated periumbilical veins, hemorrhoids, asterixis, edema, and testicular atrophy, gynecomastia, or loss of pubic and axillary hair may all be signs of liver disease.

INTRODUCTION

Liver function tests routinely combine markers of function (albumin and bilirubin) with markers of liver damage (alanine transaminase, alkaline phosphatase, and alpha glutamyl transferase). Abnormalities in liver enzyme activities give useful information about the nature of the liver insult a predominant rise in alanine transaminase activity (normally contained within the hepatocytes) suggests a hepatic process. Serum transaminase activity is not usually raised in patients with obstructive jaundice, although in patients with common duct stones and cholangitis a mixed picture of raised biliary and hepatic enzyme activity is often seen.

Epithelial cells lining the bile canaliculi produce alkaline phosphatase, and its serum activity is raised in patients with intrahepatic cholestasis, cholangitis, or extrahepatic obstruction, increased activity may also occur in patients with focal hepatic lesions in the absence of jaundice. In cholangitis with incomplete extrahepatic obstruction, patients may have normal or

slightly raised serum bilirubin concentrations and high serum alkaline phosphatase activity.

Serum alkaline phosphatase is also produced in bone, and bone disease may complicate the interpretation of abnormal alkaline phosphatase activity. If increased activity is suspected to be from bone, serum concentrations of calcium and phosphorus should be measured together with 5-nucleotidase or alpha glutamyl transferase activity, these two enzymes are also produced by bile ducts, and their activity is raised in cholestasis but remains unchanged in bone disease. Occasionally, the enzyme abnormalities may not give a clear answer, showing both a biliary and hepatic component. This is usually because of cholangitis associated with stones in the common bile duct, where obstruction is accompanied by hepatocyte damage as a result of infection within the biliary tree.

Rational and reliable liver diagnostics requires the simultaneous application of certain liver tests for ascertaining important parameters of cellular integrity and essential liver functions. In some cases, they have to be complemented by further specific tests. Under normal conditions and during physiological moulting, hepatocytes leak minor quantities of enzymes, which are detectable in the serum as normal values. A shift in the normal enzyme pattern is termed enzyme distortion. It is possible to derive various kinds of information from the prevailing enzyme pattern. Due to inflow - enzyme secretion from the liver cell and outflow - enzyme elimination, these values are kept largely constant within a normal range.

METABOLIC FUNCTIONS OF THE LIVER

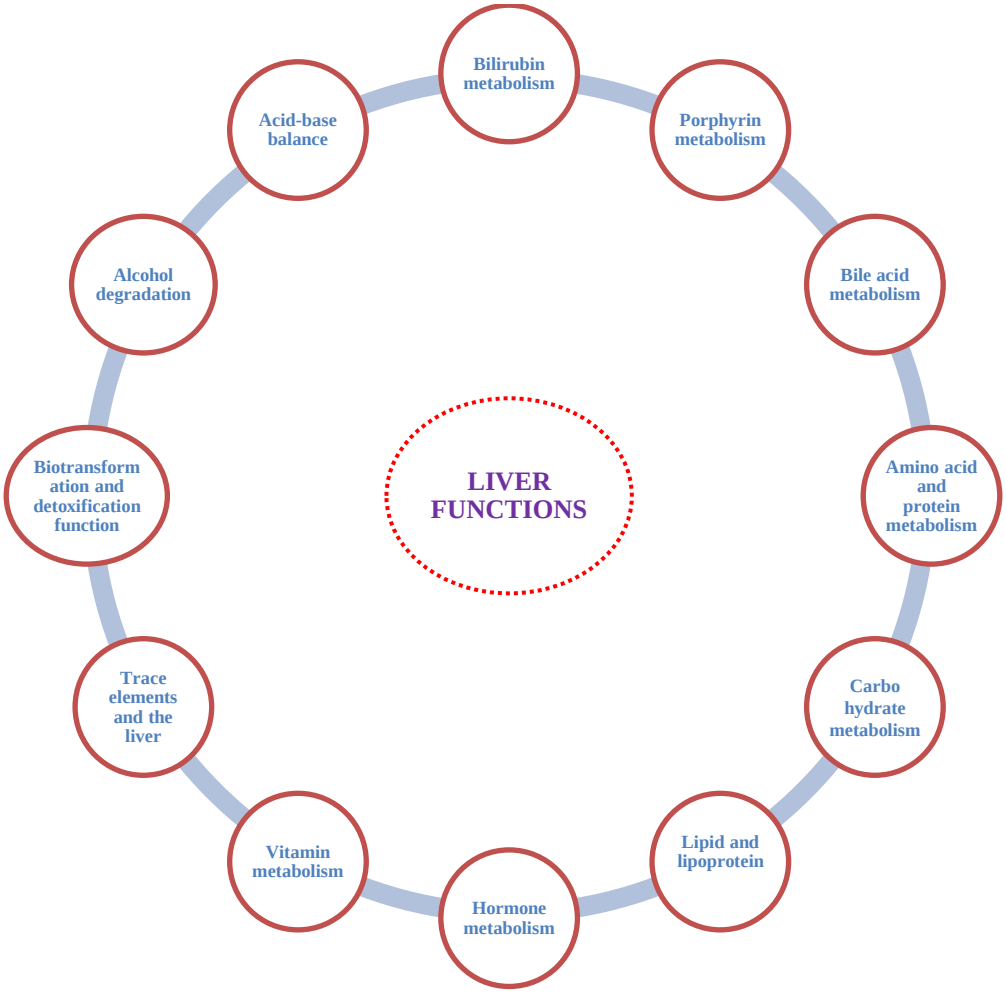

Fig. 1 Metabolism Functions of Liver

HOSPITAL MEDICINE CLINICS CHECKLIST

1. In the setting of abnormal liver function tests (LFTs), review [2] history for liver disease risk factors (alcoholism, blood transfusion, intravenous drug use, current hepatotoxic medications, or family history of liver disease).
2. In patients with liver injury, review risk factors and history along with pattern of LFTs to narrow your differential.
3. For patients with abnormal LFTs, recheck alanine transaminase, aspartate transaminase, alkaline phosphatase, bilirubin, and albumin levels in 1 to 3 months.
4. Also screen for treatable causes of hepatitis if abnormal LFTs persist for more than 6 months: hemochromatosis; autoimmune hepatitis; a1-antitrypsin deficiency; hepatitis B, C, and D; non-alcoholic fatty liver disease; and Wilson disease.
5. Check g-glutamyl transferase level in patients with increased alkaline phosphatase levels to confirm hepatic origin of the enzyme.
6. If total bilirubin levels are increased, direct and indirect bilirubin fractions should be obtained. If indirect fraction is greater than 80% of total, then order a reticulocyte count and peripheral smear to exclude hemolysis.
7. Consider liver biopsy for any patient with abnormal LFTS of more than 6 months duration.

NORMAL VALUES FOR LFTS

Table 1 LFT Normal Values

ALT	AST	ALP	BILIRUBIN	INR	ALBUMIN
0 to 45 IU/L	0 to 45 IU/L	30 to 120 IU/L	0.5 to 1.0 mg/dL	10.9 to 12.5 sec	4 to 6 g/dL

Normal LFTs are defined as the mean distribution 2 standard deviations in a representative healthy population. Therefore, statistically, 5% of all healthy individuals have abnormal liver function studies, many of which may be of no clinical significance. The interpretation of all abnormal liver chemistries must be considered in the clinical context of a given patient.

DIFFERENT TYPES OF LIVER INJURY

Hepatocellular injury

Cellular injury in the liver, causing release and increase of AST and ALT levels out of proportion to increase in ALP [3] levels.

Cholestatic injury

Stasis of bile flow from liver to the duodenum, causing increase in the ALP level out of proportion to increase in transaminase levels.

Mixed

Increase of AST/ALT and ALP levels are not mutually exclusive, and mixed-type injuries are often found. Also, bilirubin levels can be increased in either hepatocellular or cholestatic injury.

SIGNIFICANCE OF INCREASE OF THE DIFFERENT TYPES OF LFTS

Increased Aminotransferase (ALT/AST) Levels

Aminotransferases participate in gluconeogenesis by catalysing the transfer of amino groups from aspartic acid or alanine to ketoglutaric acid to produce oxaloacetic acid and pyruvic acid. ALT is found in its highest concentrations in the liver and is more specific to the liver than is AST, which is found in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and red cells. Increased AST levels are therefore less sensitive and specific for liver injury.

Increased ALP Levels

ALP is associated with cellular membranes, and increased levels may be caused by injury to the liver, bone, kidneys, intestines, placenta, or leukocytes. In the liver, the enzyme is located in the bile canaliculi. Biliary obstruction increases synthesis of ALP, resulting in increased plasma levels.

Increased g-Glutamyl Transferase Levels

g-Glutamyl transferase (GGT) is a sensitive marker of cholestasis, which is more specific to the liver than is ALP, although it is also produced in small amounts by the heart, brain, spleen, and seminal vesicles. It is often checked to confirm a biliary source of ALP increase.

Increased Bilirubin Levels

Bilirubin is formed from the lysis of red cells within the reticuloendothelial system. Unconjugated bilirubin is transported to the liver loosely bound to albumin. It is water insoluble and therefore cannot be excreted in urine. In the liver, bilirubin is then conjugated with glucuronic acid by the enzyme glucuronyl transferase, making it soluble in water. Any disruption in this process can cause the bilirubin to be increased.

Increased INR

The synthesis of coagulation factors is an important function of the liver. The INR measures the rate of conversion of prothrombin to thrombin and thus reflects a vital synthetic function of the liver. Vitamin K is required for the gamma carboxylation of these factors. INR may therefore be prolonged in vitamin K deficiency, warfarin therapy, liver disease, and consumptive coagulopathy.

Decreased Albumin Levels

Albumin synthesis is an important function of the liver. With progressive liver disease, serum albumin levels decrease, reflecting decreased synthesis. Albumin levels are dependent on several other factors, such as nutritional status, catabolism, hormonal factors, and urinary and gastrointestinal losses. In the setting of liver disease, albumin concentration does correlate with overall patient prognosis.

Table 2 Common Medications that may Adversely Affect LFTs

Cholestatic Pattern	Hepatocellular Pattern
Amoxicillin/clavulanic acid	Acarbose
Anabolic steroids	Acetaminophen
Chlorambucil	Allopurinol
Chlorpropamide	Amiodarone
Clopidogrel	L-Asparaginase
Erythromycin estolate	Aspirin and nonsteroidal anti-inflammatory drugs
Estrogen	Carbamazepine
Methimazole	HAART (highly active antiretroviral therapy) drugs
Mirtazapine	Halothane
Phenobarbital	Hydralazine
Terbinafine	Imipramine
	Isoniazid
	Ketoconazole

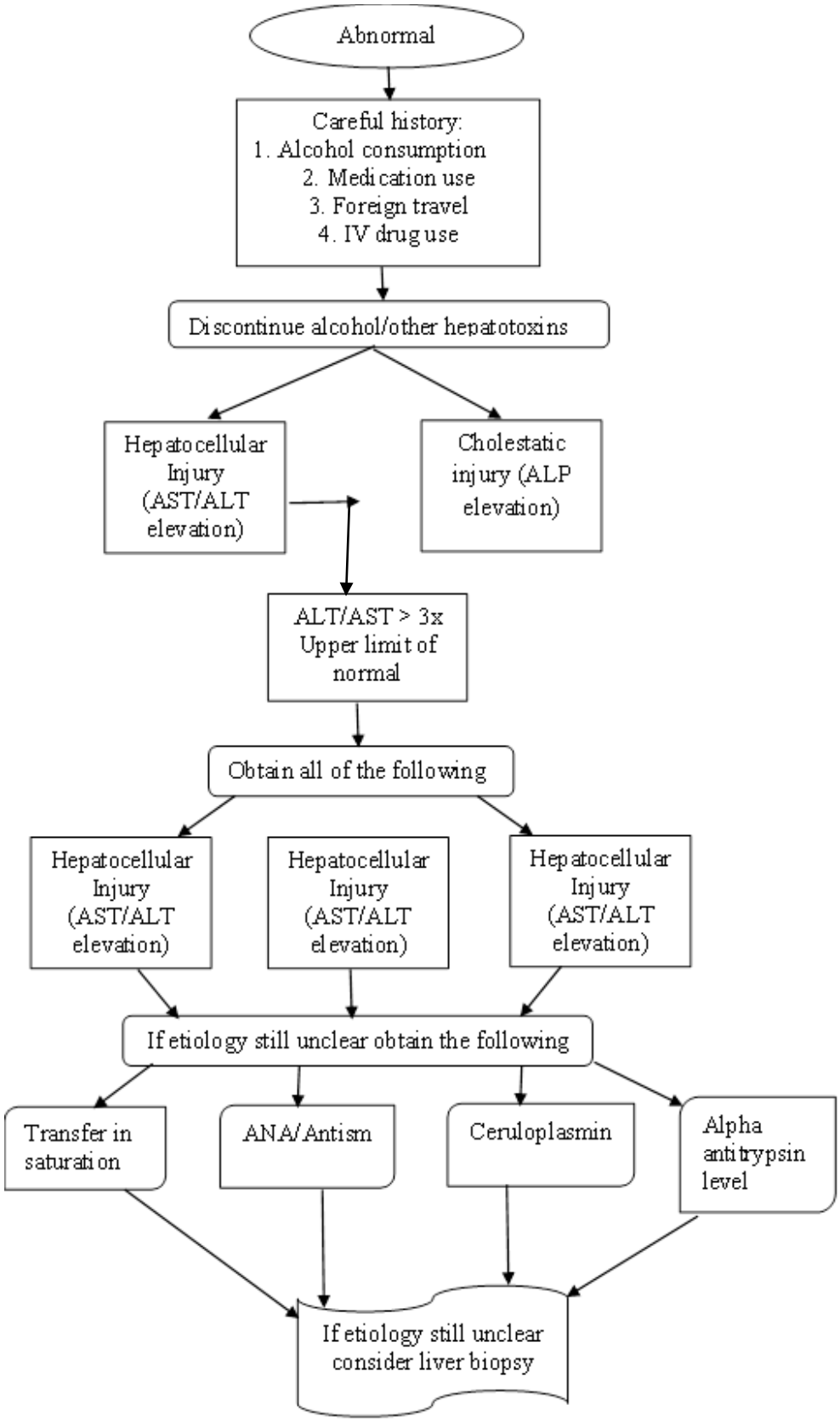

Fig. 2. Evaluation of patient with abnormal LFTs

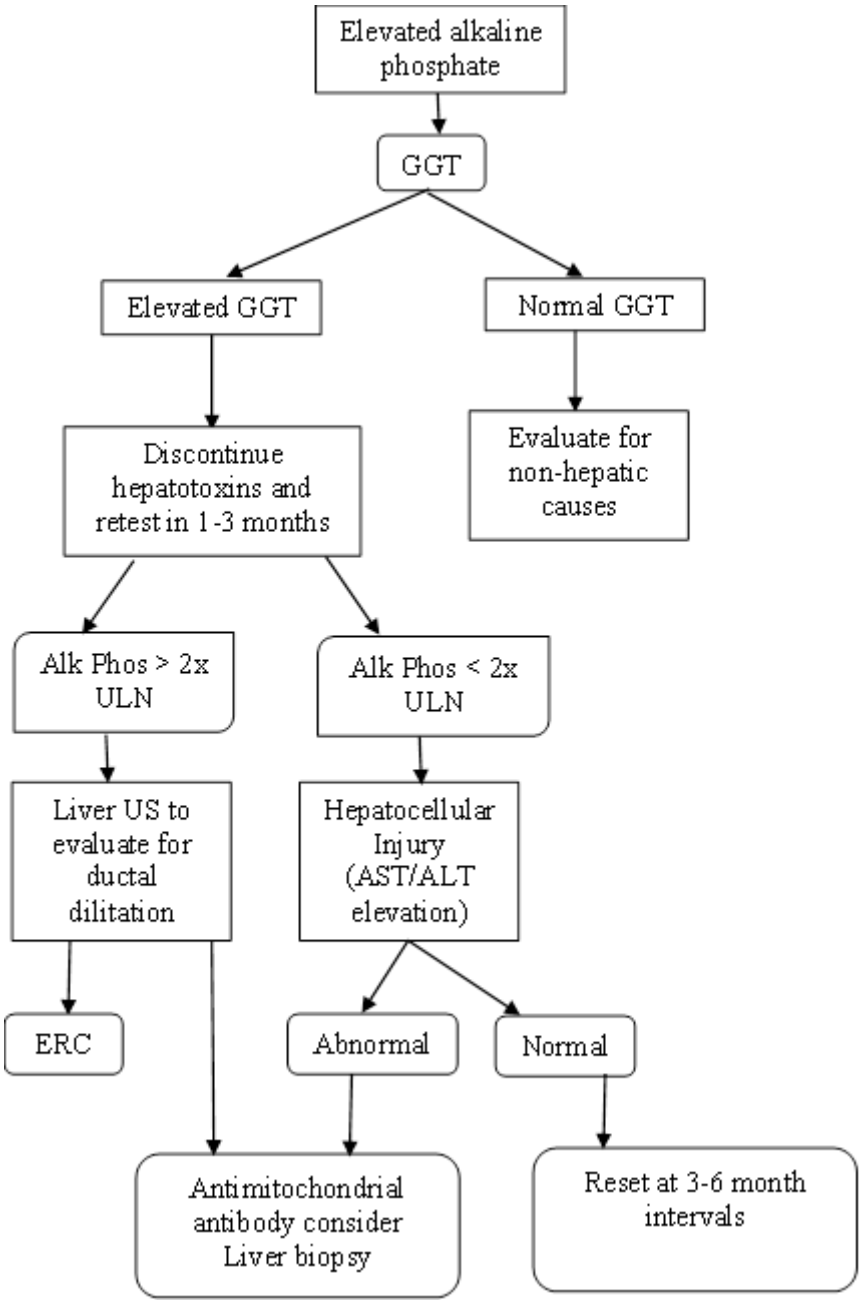

Fig. 2 (Continued)

CONCLUSION

The magnitude of liver enzyme increase may affect the decision to delay further evaluation. There are no guidelines to dictate management, but we propose immediately proceeding with further diagnostic investigation if AST/ALT levels are more than 3 times normal or if ALP levels are more than 2 times normal. Otherwise, further testing may be delayed. If low-level enzyme increase is discovered in the hospital setting, and further testing is to be delayed, ensure appropriate communication with the primary physician on discharge. Liver biopsy should be considered for any patient with abnormal LFTs that persist for more than 6 months. A biopsy sample should be obtained before the end of the 6-month period if the patient's condition deteriorates. Liver biopsy is the only definitive means of establishing a diagnosis of chronic hepatitis.

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