Approach to Impaired Liver Function Tests

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Abstract: Initially, it is important to make distinction between liver function and liver enzyme which include, serum aminotransferases level and alkaline phosphatase level. Their elevations indicate hepatocyte and bile duct epithelial injury. However, albumin, bilirubin and prothrombin time are measures of hepatic function. But, these are affected by extrahepatic factors such as nutrition, hemolysis and antibiotic use.

Keywords: Liver function tests (LFTs); Aspartate transaminase (AST); Alanine aminotransferase (ALT); alkaline phosphatase (ALP); G Glutamyl transpeptidase (GGT).

1. Introduction

Standard laboratory tests for liver function are often requested by doctors in patients with non-specific symptoms such as tiredness, abdominal pain, dyspepsia, and weight loss. Considerable uncertainty exists as to the appropriate follow up of mildly abnormal results in patients with no signs suggestive of liver disease.¹⁻²

Aminotransferases are among the most wildly used tests and not specifically to the liver, although they are widely used as liver enzymes. Aspartate transaminase (AST) is found in liver, muscle, heart, kidney, red cell and brain. Alanine aminotransferase (ALT) little more specific to the liver, and found in muscle and kidney.¹⁻³ ALT is thought to be more specific for hepatic injury because it is present primarily in the cytosol of the liver and in low concentrations elsewhere. AST has cytosolic and mitochondrial forms and is present in the cytosol of the liver and in low concentrations elsewhere. AST has cytosolic and mitochondrial forms and is present in the cytosol of the liver and in low concentrations elsewhere. ALT is less commonly referred to as serum glutamicoxaloacetic transaminase and ALT asserum glutamic pyruvic transaminase.¹⁻³

Blood tests commonly obtained to evaluate the health of the liver include liver enzyme levels alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transferase, tests of hepatic synthetic function (albumin, prothrombin time/international normalized ratio (INR)), and the serum bilirubin level.¹⁻⁴

The initial evaluation of a patient with abnormal liver biochemical and function tests (LFTs) includes obtaining a history to identify potential risk factors for liver disease and performing a physical examination to look for clues to the etiology and for signs of chronic liver disease. Subsequent testing is determined based on the information gathered from the history and physical examination as well as the pattern of LFT abnormalities.¹⁻⁶

The child-Pugh score is the best indicator of liver function in patient with cirrhosis and MELD score measures more than liver function.⁷⁻¹⁰ The Child-Pugh score is still considered the cornerstone in the prognostic evaluation of cirrhotic patients although it was formulated more than 30 years ago. Nevertheless, it has some drawbacks such as subjectivity of clinical parameters and limited discriminateability.¹⁻⁷⁻¹⁰ Child-Pugh class A patients usually show good medium-term survival without orthotrophic liver transplantation (OLT) unless other events (for example, hepatocellular carcinoma, uncontrolled bleeding due to portal hypertension, etc) occur,¹⁰ while Child-Pugh class C patients are considered the conventional candidates for the procedure. Child-Pugh class B patients can be considered a heterogeneous group as their clinical condition may remain stable for more than a year or rapidly deteriorate.⁷⁻¹¹

MELD scoring system is useful for predicting prognosis in patients with liver cirrhosis and is correlated with residual liver function. It predictor of both short and medium term survival, and performs at least as well as the Child-Pugh score. An increase in MELD score is associated with a decrease in residual liver function.¹² The Model for End-Stage Liver Disease (MELD) consists of serum bilirubin and creatinine levels, International Normalized Ratio (INR) for prothrombin time, and etiology of liver disease.¹² Recently, the model for end stage liver disease (MELD) was introduced as a tool to predict mortality risk and to assess disease severity in patients with liver cirrhosis so as to determine organ allocation priorities.¹² Although previously formulated as a prognostic index for cirrhotic patients undergoing transjugular intrahepatic portosystemic stentshunt (TIPSS), it was validated by the same authors on a broad series of patients with liver disease of various aetiology and severity.¹₃⁻¹⁴ Nevertheless, although the MELD score takes into consideration objective parameters (serum creatinine, the international normalized ratio (INR), bilirubin levels), and is computed with statistically derived coefficients on a continuous scale with no upper or lower limits, thus avoiding many drawbacks of the Child-Pugh score, it has generated some criticism.¹₅⁻¹₆

2. Properties

Alanine aminotransferase (ALT) exclusively in cytoplasm whereas aspartate transaminase (AST), is both cytoplasm and mitochondrial.
The half life of total AST is 17 +/- 5 hours, whereas ALT is 47 +/-10 hour. AST/ALT ratio depend on gender, age and sex.\textsuperscript{[1,17]}

The aminotransferases (formerly transaminases) are the most frequently utilized and specific indicators of hepatocellular necrosis. These enzymes— aspartateaminotransferase (AST, formerly serum glutamateoxaloacetic transaminase-SGOT) and alanine aminotransferase (ALT, formerly serum glutamic pyruvateaminotransferase-SGPT) catalyze the transfer of the $\alpha$ amino acids of aspartate and alanine respectively to the $\alpha$ ketogroup of ketoglutaric acid. ALT is primarily localized tohe liver but the AST is present in a wide variety of tissues like the heart, skeletal muscle, kidney, brain and liver.\textsuperscript{[18,19]}

Alkaline phosphatases are a family of zinc metaloenzymes, with a serine at the active center; they release inorganic phosphate from various organic orthophosphates and are present in nearly all tissues. In liver, alkaline phosphatase is found histochemically in the microvilli of bile canaliculi and on the sinusoidal surfaces of hepatocytes. Alkaline phosphatase from the liver, bone, and kidney are thought to be from the same gene but that from intestine and placenta are derived from different genes.\textsuperscript{[20]}

G-Glutamyl transpeptidase (GGT) or 5nucleotidase can help hepatic vs. nonhepatic source because of elevated parallel to alkaline phosphatase. Alkaline phosphatase elevated physiologically in whom less than 18 years old, or pregnant woman.\textsuperscript{[21]}

The classification of bilirubin into soluble and thus allows it to be excreted into the urine. Normally total serum bilirubin is measured; however, the unconjugated and conjugated portions can be determined by measures of the fractions of indirect bilirubin and direct bilirubin respectively.\textsuperscript{[45]}

The classification of bilirubin into direct and indirect bilirubin are based on the original van der Berg’s method of measuring bilirubin. Bilirubin is altered by exposure to light so serum and plasma samples must be kept in dark before measurements are made.\textsuperscript{[19]}

3. Patterns of Liver Disease

The abnormal liver enzymes are characterized by either acute or chronic of cut off six month which is either hepatocellular or cholestatic or mixed. Injury to the liver, whether acute or chronic, eventually results in an increase in serum concentrations of aminotransferases.\textsuperscript{[1,48]}

Based on the pattern of albumin mRNA and RNA in hepatocytes.\textsuperscript{[18]}

Prothrombin time (PT) does not usually include in the LFs panel. Abnormal PT prolongation may be a sign of serious liver dysfunction. An elevated PT can result from a vitamin K deficiency, a trial of vitamin K injections is the most practical way to exclude vitamin K deficiency in such patients.\textsuperscript{[1,2,30-35]}

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Albumin synthesis is affected not only in liver disease but also by nutritional status, hormonal balance and osmotic pressure. The serum levels are typically depressed in patients with cirrhosis and ascites. In patients with or without ascites, the serum albumin level correlates with prognosis.\textsuperscript{[16]}

In addition the rate of albumin synthesis has been shown to correlate with the Child-Turcotte or Child-Pugh score.\textsuperscript{[22]}

Corticosteroids and thyroid hormone stimulate albumin synthesis by increasing the concentration
of the serum liver chemistry abnormalities, serum liver chemistry tests can be classified to provide a practical approach for the evaluation and diagnosis of hepatobiliary diseases. For the purpose of this document, we have classified the analysis of liver chemistry abnormalities to the interpretation of serum ALT and aspartate aminotransferase (AST) abnormalities (hepatocellular injury) and serum alkaline phosphatase and bilirubin abnormalities (cholestatic pattern). Although it is important to emphasize that liver chemistest abnormalities frequently occur in overlapping patterns, presenting an obvious limitation to this type of categorized analysis, the division of liver chemistry abnormalities into “hepatocellular injury” and “cholestatic” patterns allows a commonly used, simplified approach for the interpretation of serum liver chemistries. In addition, elevations of the hepatic alkaline phosphatase with minimal or no elevations of the serum ALT, AST, or bilirubin may also be indicative of “infiltrative” diseases of the hepatic parenchyma. Blood tests in such asserum albumin and prothrombin time are also important determinants of hepatic synthetic function, but are not specific for hepatic disease. Nonetheless, these tests have essential role in the evaluation of the hepatic function of patients with acute or chronic liver diseases.

Although levels of ALT and AST can be extremely elevated (exceeding 2,000 U per L in cases of hepatocyte injury and necrosis related to drugs, toxins, ischemia, - related, herpes simplex virus, acetaminophen, and hepatitis. However, fatty liver, hemochromatosis and alpha one antitrypsin deficiency are the etiology of chronic liver. The both acute and chronic hepatitis etiology include autoimmune, Wilson’s Disease, hepatitis B, Budd-Chiari syndrome, alcoholic liver disease and medication. The cause of extrahepatic liver disease is stone, cancer, sphincter dysfunction and cholelithiasis or trauma. The cause of intrahepatic cholestasis disease are primary biliary cirrhosis, cholangitis, sepsis, drugs, granulomas, total parenteral nutrition, and metastases. While both intra and extrahepatic liver disease are primary sclerosing cholangitis, cholangiocarcinoma and radiation.

4. Clinical Value of Different Patterns & Level

In almost all liver disease, ALT is higher than AST except in alcoholic liver disease and advanced liver fibrosis. In alcoholic hepatitis, AST is greater than ALT. Alcohol increases mitochondrial AST and decrease cytoplasmic ALT. ALT is also low due to pyridoxine deficiency.

AST and ALT are significantly lower in patients with renal failure.

Normal ALT in patients with hepatitis C virus (HCV) may still be associated with abnormal hepatic histology. Level less than 300U/L in chronic HCV/HBV, NAFLD and hemochromatosis. ALT more than 150 or AST more than 300U/L is uncommon in alcoholic liver disease. Aminotransferase can be elevated in the context of other abnormalities with raised bilirubin such as hemolysis, Gilbert’s, and obstruction. In Wilson’s will found very high level of aminotransferases and hemolysis. However, very high level of aminotransferases with new onset ascites found in cardiac or Budd-Chiari. Very high level of aminotransferases and LDH found in ischemic hepatitis, with high CPK in rhabdomyolysis. The ratio of AST to ALT has some clinical utility, but has important limitations. In many forms of acute and chronic liver injury or steatosis (fatty infiltration of the liver), the ratio less than or equal to 1. This is particularly true in patients with hepatitis C. However, an AST/ALT ratio greater than 2 characteristically present in alcoholic hepatitis. A recent study of 140 patients with nonalcoholic steatohepatitis (NASH; confirmed by liver biopsy) oralcoholic liver disease found a mean AST/ALT ratio of 0.9 in patients with NASH and 2.6 in patients with alcoholic liver disease. Within the population studied, 87 percent of patients with an AST/ALT ratio of 1.3 or less had NASH (87 percent sensitivity, 84 percent specificity). The severity of NASH as measured by the degree of fibrosis increased, as did the AST/ALT ratio. A mean ratio of 1.4 was found in patients with cirrhosis related to NASH. Wilson’s disease, a rare problem, can cause the AST/ALT ratio to exceed 4.5. While these ratios are suggestive of certain conditions, there is too much overlap between groups to rely on them exclusively when making a diagnosis.

The AST and ALT levels are increased to some extent in almost all liver diseases. The highest elevations occur in severe viral hepatitis, drug or toxin induced hepatic necrosis and circulatory shock. Although enzyme levels may reflect the extent of hepatocellular necrosis they do not correlate with eventual outcome. In fact declining AST and ALT may indicate either recovery of poor prognosis in fulminant hepatic failure. The AST and ALT are moderately elevated in acute hepatitis, neonatal hepatitis, chronic hepatitis, autoimmune hepatitis, drug induced hepatitis, alcoholic hepatitis and acute biliary tract obstructions. The ALT is usually more frequently increased as compared to AST except in chronic liver disease. In uncomplicated acute viral hepatitis, the very high initial levels approach normal levels within 5 weeks. The onset of illness and normal levels are obtained in 8 weeks in 75% of cases. For reasons, which are not, understood AST levels appear disproportionately low in patients with Wilson disease.

The ratio of AST to ALT is of use in Wilson disease, chronic liver disease (CLD) and alcoholic liver disease and a ratio of more than 2 is usually observed. The lack of ALT rise is probably due to pyridoxine deficiency. In NASH the ratio is less than one in the absence of fibrosis on liver biopsy.

In viral hepatitis the ratio is usually less than one. Theratio invariably rises to more than one as cirrhosis develops possibly because of reduced plasma clearance of AST secondary to impaired function of sinusoidal cells. ALT exceeds AST in toxic hepatitis, viral hepatitis, chronic active hepatitis and cholestatic hepatitis.

5. Conclusion

Liver biochemistries are among the most widely ordered test in clinical practice. Aminotransferases and alkaline phosphatase are not liver function test. Patterns of their elevation are significant utility at the bedside. Finding the
way through the multiple diagnostic pathways can challenge even the experienced clinician. Knowledge of the pathophysiology of liver enzymes is an essential guide to understanding their alteration. The pattern of enzyme abnormality, interpreted in the context of the patient’s characteristics, can aid in directing the subsequent diagnostic work-up. Awareness of the prevalence of determined liver disease in specific populations and of possible hepatic involvement during systemic illnesses or drug therapies may help the clinician identify the cause of alterations efficiently. Child's score is most widely used for assessing the liver function.

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