

# Approach to Liver Function Tests in Children

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The liver is a multifactorial organ which is involved in a number of critical excretory, synthetic and metabolic functions. Although the term 'liver function test' is commonly used, it is imprecise since many of the tests, such as transaminase, do not measure liver function. Therefore, these tests should be referred to as 'liver enzyme tests', and 'liver function tests' should be the term used to measure hepatocyte synthetic functions, such as serum albumin and prothrombin time. Furthermore, commonly used biochemical tests may be normal in a patient with liver disease (compensated cirrhosis) or be abnormal in a case with a healthy liver. In this article different aspects of liver function tests and the approach to abnormal liver function tests are reviewed.

**Keywords:** Liver Disease; Children; Tests

## 1. Introduction

Abnormal liver function tests (LFTs) are frequently seen in asymptomatic patients, as many screening test panels now include them routinely (1). On the other hand, individual patients can have baseline fluctuations in serum aminotransferase levels. In a large cross-sectional population based study, more than 30% of adults with abnormal LFTs, had normal tests upon retesting (2). The sensitivity and specificity of the serum aminotransferases, used to discriminate those with and without liver disease, depend on the cutoff values chosen to define an abnormal test (3). There is wide variability in what is considered to be the upper limit of normal for alanine aminotransferase (ALT) across different laboratories. The most sensitive cutoff for ALT in adults is 29 IU/L for men and 22 int./unit/L women (4).

There are some limitations with LFT, which include: (5, 6).

- 1) A normal LFT does not ensure that the patient is free of liver disease (e.g. compensated cirrhosis).
- 2) These tests are not specific for liver function.
- 3) These tests do not usually provide a specific etiology, but are indicative of a liver disorder.

Therefore the clinical significance of any abnormal LFT must be interpreted in each individual patient's case.

Tests that evaluate liver function can be divided into five categories:

- 1) Those that indicate liver injury (liver enzymes, ALT, and aspartate aminotransferase (AST)).

- 2) Those that indicate impaired bile flow or cholestasis (alkaline phosphatase, gamma glutamyl transpeptidase, GGT and 5'-nucleotidase).

- 3) Tests that indicate impaired liver synthetic functions (serum albumin, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR) and factor VII and V).

- 4) Tests that show impaired hepatic excretory functions (bilirubin, bile acids).

- 5) Tests that show hepatic metabolic functions, indicating the role of the liver in detoxification and clearance of endogenous metabolites, such as ammonia.

Considering the above mentioned tests, liver enzymes AST, and ALT, which are the most commonly ordered tests in patients with liver disease, do not really indicate liver function as they only show liver damage. Furthermore, there is no direct relationship between the levels of these enzymes and the degree or severity of liver damage. Both AST and ALT are normally present in the serum at low levels in healthy populations. There is also a strong correlation between serum ALT levels and body mass index (BMI). AST is present as both cytosolic and mitochondrial isoenzymes and it is also found in high concentrations in a number of different tissues including; liver, heart muscle, skeletal muscles, kidney, brain, pancreas, lungs, leukocytes and red blood cell (RBC). ALT is a cytosolic enzyme that is present at highest concentrations in the liver. The ratio of AST to ALT may indicate specific diseases (e.g. AST

### Implication for health policy/practice/research/medical education:

Since commonly used biochemical tests, referred to as liver function tests, may be normal in a patient with liver disease or abnormal in a patient with a healthy liver, the approach taken to liver function tests is very important, particularly in children. This paper reviews the different aspects of liver function tests.

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> ALT), and it is usually seen in patients with Wilson's disease and those with fatty liver or chronic hepatitis C virus (HCV) liver diseases (7, 8). An isolated disproportionately increased AST level may indicate; hemolysis (including difficult venipuncture), acute rhabdomyolysis (during viral illnesses), myopathies, myocardial disease, or recent rigorous physical activity (long duration running or weight lifting) (9, 10). Considering the above mentioned sources of transaminases, the causes of isolated AST and ALT elevation can be categorized into two groups; hepatic and nonhepatic.

## 2. Hepatic Causes

The hepatic causes are also divided into two groups; hepatocellular injury and biliary disease (cholestasis). Patients with hepatocellular damage generally have a disproportionate elevation of serum aminotransferase, compared with alkaline phosphatase, while those with cholestasis have the opposite pattern. In patients with liver or biliary disease, in addition to enzyme elevation, other components of a LFT, including; bilirubin, albumin and PT, INR may also be changed. In suspected cases of hepatobiliary disease the following causes must be considered (11-14):

1) Viral hepatitis (HAV, HBV, HCV, HDV, HEV, and other possible viral, bacterial, or parasitic infections).

2) Medications: Almost any medication can cause an elevation of liver enzymes.

The most common drugs are nonsteroidal anti-inflammatory drugs (NSAIDs); anti-tuberculosis; antibiotics; anticonvulsants and statins. In addition, herbal medications must also be considered as causes of liver enzymes elevation. Therefore, a careful history of any type of medication use may be critical in identifying medication as the causes of elevated liver enzymes.

3) Alcohol abuse: This is a common finding in adults. In these cases the AST to ALT ratio is usually more than 2/1.

4) Hepatic steatosis and steatohepatitis: These conditions are common causes of mild (less than 5 times) transaminase elevation in children and adults. The differentiation between steatosis and steatohepatitis (NASH) requires a liver biopsy.

5) Autoimmune hepatitis (AIH) may present with isolated liver enzyme elevation, therefore in any case with unexplained prolonged liver enzyme elevation, AIH must be considered, and a liver biopsy is needed for confirmation and before starting treatment.

6) Wilson's disease: Patients with Wilson's disease may present with isolated aminotransferase elevation without clinical symptoms.

7) Glycogen storage disease (GSD) may present with isolated liver enzyme elevation, without clinical symptoms, usually after six months of age.

8) Hemochromatosis is a common genetic disorder, usually seen in adults, which may present with isolated liver enzyme elevation.

9) Alpha-1 antitrypsin deficiency, according to some re-

ports, this is the most common metabolic cause of liver disease in infants and children, and it may present with isolated liver enzyme elevation.

10) Biliary disease: Patients with biliary disease may present with isolated liver enzyme elevation.

In those with biliary disease, there is a significant elevation of alkaline phosphatase and gamma glutamyl transferase (GGT), which is the best guide for differentiating hepatobiliary disease from extrahepatic causes. Sometimes very high levels of ALT and AST (> 15 times normal) are seen with acute viral hepatitis, medications, toxin induced hepatotoxicity or following an acute episode of hypoxia or hypoperfusion (shock liver) (15, 16). In cases of shock liver, there is also a significant elevation of LDH, which makes this condition different from other causes of very high levels of liver enzymes. Aminotransferases are one of the most important means of following patients with acute and chronic hepatitis and their response to medical therapy.

## 3. Other Parameters of Liver Function Tests

### 3.1. Alkaline Phosphatase

Alkaline phosphatase (ALP) is found in several tissues, including; the canalicular membrane of hepatocytes, bone osteoblasts, small intestine enterocytes, proximal tubules of kidneys, the placenta and white blood cells. The precise function of liver ALP is not known, although it may participate in transport processes. The serum level of ALP varies considerably with age. Normal growing children and rapidly growing adolescents in particular have high serum ALP of bone origin. This condition is also known as transient hyperphosphatasemia of infancy, which is a benign condition characterized by marked transient increased levels of ALP in an infant or child younger than five-years-of-age without any liver disease or bone problem (17, 18). The rise in ALP is quite dramatic, often exceeding ten times the upper limit of the laboratory, and then it returns to normal within a few weeks or months. In a case with high ALP the best indicator of hepatobiliary disease is a concomitant elevation of gamma glutamyl phosphatase (GGT) and 5' nucleotidase (19). Therefore, an isolated increased ALP does not indicate liver or biliary disease, if other liver biochemical tests are normal. The differential diagnosis of increased serum ALP in the absence of liver disease include: pregnancy, familial inheritance, chronic renal failure, blood groups B or O, and transient hyperphosphatasemia in infancy. A low ALP serum level is found in zinc deficiency and Wilson's disease.

## 4. Serum Proteins

### 4.1. Albumin

Albumin is the principle serum protein and it is syn-

thesized only in the liver. This protein is synthesized in the rough endoplasmic reticulum of hepatocytes at a rate of 150 mg/kg/d and it has a half-life in serum of about 20 days. Considering the long half-life, low serum albumin often indicates chronic liver disease. On the other hand, in cases of liver disease with increased globulin and normal albumin, this indicates an infectious process or autoimmune hepatitis. However, patients with compensated chronic liver disease may have normal levels of serum albumin. Hypoalbuminemia is not specific for liver disease, because it may also occur in the presence of malnutrition, protein losing enteropathy, chronic infection and nephrotic syndrome.

#### 4.2. Coagulation Factors

Abnormal hemostasis is a common finding in patients with liver disease due to diminished hepatic synthesis of coagulation factors V, VII, IX, X and XI prothrombin, fibrinogen and vitamin K deficiency due to inadequate intake or malabsorption, and dysfibrinogenemia (14, 20). Due to the large functional reserve of the liver coagulation disorders it may not be seen with mild to moderate liver disease, but they are usually seen with severe acute hepatic failure or end stage chronic liver disease. Therefore, testing for a coagulation defect is not a screening procedure. Prothrombin time (PT) indicates the extrinsic pathway of coagulation and it is prolonged if any of the involved factors (I, II, V, VII and X) are deficient, either individually or in combination. A prolonged PT is not specific for liver disease, because it is seen in various conditions such as; congenital coagulation factor deficiency, disseminated intravascular coagulation (DIC), malabsorption, and ingestion of medications that affect the PT complex. Factor VIII, which is produced in tissues other than the liver, can be helpful in distinguishing between hepatic and non-hepatic causes of coagulopathy, (in the setting of normal factor VIII activity, prolonged PT indicates plasma clotting factor deficiency from impaired hepatic synthesis or secondary to vitamin K deficiency). The PT test is not a sensitive index of chronic liver disease, because in many cases even with end stage cirrhosis, levels may be normal or only slightly prolonged. On the other hand, the PT test has high prognostic value, particularly for patients with acute hepatic failure.

#### 5. Bilirubin

Conjugated hyperbilirubinemia (> 20% of total bilirubin) indicates hepatobiliary disease and it is always pathologic. It is usually accompanied by bilirubin in the urine (causes deep yellow colored urine) and it can be detected by a urine dipstick. Bilirubinuria may appear before overt clinical jaundice. In cases with acute liver disease, when the patient is not jaundiced (anicteric), there is no possibility for fulminant hepatic failure, on the other hand, the chance of hepatic failure increases with rising bilirubin levels. Therefore, the level of serum bili-

rubin can be an indicator of prognosis in patients with acute liver disorders.

#### 6. Ammonia

The concentration of ammonia in the blood is regulated by the balance of its production and clearance. Its production mainly occurs in the large intestine through the action of bacterial urease on dietary proteins and amino acids. Clearance of ammonia under normal circumstances occurs mainly by the liver through the transformation of ammonia into urea (19). Advanced liver disease is the most common cause of hyperammonemia. Patients with advanced cirrhosis may have normal fasting levels of ammonia. Conversely, the non-fasting value of ammonia may be elevated even in a patient with mild liver disease. Therefore, fasting serum levels should be determined in order to accurately reflect the clearance of ammonia in the blood (20).

#### 7. Nonhepatic Causes of Liver Enzymes Elevation

If hepatobiliary causes of liver enzyme elevation are excluded, non-hepatic causes which include; muscle disorders (14), cardiac and thyroid disease (21, 22), celiac disease, and on rare occasions, adrenal insufficiency (23, 24), should be considered and investigated. Conditions that cause muscle injury and elevated transaminase, also lead to the elevation of creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). Thyroid disorders and undiagnosed celiac disease can also produce elevated liver enzymes. Therefore, in any case with unexplained elevated liver enzymes, CPK and LDH levels, along with tests for thyroid function and celiac disease, should be carried out. Finally, in any case with persistent (usually more than three months) AST, and ALT levels greater than two fold the upper limit of normal, if the above mentioned tests are ambiguous, a liver biopsy is recommended (25, 26).

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