Mildly Elevated Transaminases (ALT, AST): Why And What To Do

Dr Vibhu V Mittal
Consultant Gastroenterologist
Department of Gastroenterology
Pushpanjali Crosslay Hospital
NCR-Delhi

Abstract
Mildly elevated transaminase is seen in up to 1-9% of population. It signifies ongoing liver injury. There are varied common and uncommon hepatic and extrahepatic causes for this. Evidence regarding the correct approach of evaluation is limited and the expert consensus is for step based approach for this problem. Detailed history and examination is of paramount importance.

With the ease of doing liver function test (LFT) due to availability of automated machines, more and more such tests are being asked for. In many such instances the result is mildly elevated liver enzymes. Mildly elevated liver enzymes in a seemingly normal individual trouble even an experienced physician. An estimated 1% to 9% of people who have no symptoms have high liver enzyme levels when screened with standard biochemistry panels. A US survey showed elevated alanine aminotransferase (ALT) in 8.9% of surveyed people from 1999 to 2002, an increase from previous reports.

Significance of Transaminases
Both aspartate aminotransferase (AST) and ALT are present in hepatocytes and are released into the blood in greater amounts when hepatocytes are damaged. ALT is predominantly present only in liver while AST is also seen in myocyte and erythrocytes. Because of this elevations in ALT are more specific for liver injury. Normally these are present in serum at low levels, usually less than 30 to 40 U/L. Although the actual values may differ from laboratory to laboratory, normal serum levels are usually less than 40 U/L for AST and less than 50 U/L for ALT.

Some of the recent studies have pointed the need to lower the values of "normal" ALT to 19 U/L for male and 30 U/L for female to increase the sensitivity of diagnosing cases of mild hepatitis. Though at these levels the specificity is compromised with increase in number of incidental abnormalities.

Anything below 5x (5 times upper limit of normal) is considered as mildly elevated. Persistent elevation has higher significance.

Causes
Asymptomatic elevation of liver transaminase levels can be categorized into common hepatic, less common hepatic, and extrahepatic causes. (Table 1).

Common Hepatic Causes
NASH - It is one of the leading cause of mildly elevated liver enzymes in asymptomatic individuals. Few of these

Table 1: Causes of mildly raised transaminases

<table>
<thead>
<tr>
<th>Hepatic causes (Common)</th>
<th>Uncommon Hepatic causes</th>
<th>Extra hepatic causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Non Alcoholic Steato Hepatitis (NASH)</td>
<td>• Auto immune hepatitis</td>
<td>• Celiac sprue</td>
</tr>
<tr>
<td>• Alcohol</td>
<td>• Wilson’s disease</td>
<td>• Hemolysis</td>
</tr>
<tr>
<td>• Viral hepatitis</td>
<td>• Hemochromatosis</td>
<td>• Muscular disorder</td>
</tr>
<tr>
<td>• Drugs and medication</td>
<td>• Alpha-1 Antitrypsin deficiency</td>
<td>• Thyroid disorder</td>
</tr>
</tbody>
</table>

Ref: Krier M, Ahmed A. Clin Liv Dis 2009
patients may progress to cirrhosis and HCC. It is common in patients with diabetes mellitus, hypertriglyceridemia and metabolic syndrome. Ultra sound, Computed tomography and Magnetic resonance imaging have good sensitivity and specificity to diagnose fat in liver but they cannot differentiate it from alcohol related fatty liver.

Alcohol: It is an important etiology of deranged liver enzyme which can be easily diagnosed with an accurate history. Imaging or even liver biopsy cannot differentiate alcoholic liver disease from NASH reliably. AST/ALT ratio >1 and raised gamma glutamyl transferase levels suggest the possibility of alcohol related liver disease.

Viral hepatitis: Hepatitis B and Hepatitis C are two important treatable causes of liver disease. These cause transient elevation of liver enzymes and testing is recommended even if repeat levels are normal. They can be diagnosed with HbsAg and Anti HCV tests respectively.

Medications: Numerous medications have been associated with elevated transaminase levels, but the true incidence of liver injury from medications is unknown. Not only the standard drugs but other xenobiotics including herbal products are also an important cause and detailed history evaluating the same is important. Eliciting all over-the-counter and prescription medications and stopping any potentially contributing agents may identify the etiology.

Table 2: Hepatotoxicity of selected drugs

- Acetaminophen - acute hepatitis
- Allopurinol - granuloma
- Azathioprine - veno-occlusive disease, nodular regenerative hyperplasia
- Diclofenac and other nonsteroidal anti-inflammatory drugs
- Hydralazine - granuloma
- Isoniazid
- Methotrexate - fibrosis
- Metyldopa
- Nitrofurantoin - autoimmune-like disease
- Quinidine - granuloma
- Statins
- Amiodarone - phospholipidosis
- Corticosteroids
- Tetracycline
- Valproic acid

Ref: Navaro VJ et al. NEJM 2006

Uncommon Hepatic Causes

Autoimmune hepatitis: Relatively uncommon. More common in females. Is also associated with other autoimmune phenomenon. Positive auto antibodies and raised immunoglobulin G levels with typical biopsy findings are diagnostic of AIH.

Wilson’s disease: It is an autosomal recessive genetic disease of copper metabolism. The frequency of this is 1:30000 in general population. Presence of Kayser Fleisher (KF) ring on ophthalmological examination is suggestive. Diagnosis can be established with low ceruloplasmin levels and high 24 hr urinary copper levels.

Studies of Mild Aminotransferase Elevations

Only a few studies have documented the results of a thorough evaluation of patients with mildly elevated aminotransferase levels. These various studies which included detailed evaluation including liver biopsies showed, that in patients in whom apparent diagnosis could not be made after first and second line investigation; NASH is the most common etiology in these cases. A large proportion of cases could not be diagnosed even after liver biopsy. Compensated cirrhosis is diagnosed in significant proportion of patients.

But these studies were from an era prior to introduction of serological testing of hepatitis C, moreover diagnosis of NASH had inconsistencies in between various studies.

Approach to Patient

As is clear with previous discussion, the data dealing with the issue is scarce and most is retrospective in nature. There is also limited evidence on the most efficient evaluation of asymptomatic patients with mildly elevated liver transaminase levels, so present consensus is to adopt a stepwise approach based on the prevalence of each potential etiology.

Step 1 – History and Physical examination

Detailed history with emphasis on personal history of alcohol consumption and drug history is paramount for evaluation. Presence of chronic liver disease merit expedited work up for cause and confirmation of cirrhosis. History and examination looking for obesity and
metabolic syndrome may suggest possibility of NASH. History of previous surgeries, blood transfusion, IV drug abuse etc. may suggest possibility of viral hepatitis. History of other auto immune phenomenon in a lady may point towards auto immune hepatitis and a family history of liver disease especially pointing towards a autosomal recessive inheritance pattern may suggest wilson’s disease. Detailed physical examination especially looking for evidence of chronic liver disease (parotid swelling, loss of axillary hair, gynaecomastia, palmar erythema, dupytren’s contracture, dilated abdominal veins, ascites or testicular atrophy) should be done.

Even if there is no significant history or examination findings, testing for Hepatitis B (HbsAg) and Hepatitis C (Anti HCV) is recommended.

With all negative evaluation on history and physical examination and negative viral markers, patient should be kept in follow up with repeat measurement of ALT and AST after a duration of 3-4 weeks. This is because in
many instances there may be a transient elevation of liver enzymes due to a variety of identified or unidentified factors such as inadvertent drug ingestion or bystander hepatitis due to systemic illness etc. This is based on clinical evidence from a recent trial by Lazo M et al from a European centre in which it was shown that more than 30% of adults had normal enzyme levels on retesting after a median of 17.5 d.

Step 2 – Rule out common causes
With negative initial evaluation and persistently elevated enzymes on repeat LFT, further evaluation is warranted. A study conducted by National health and nutrition survey had shown that Hepatitis B, Hepatitis C and hemochromatosis were responsible for 31% of such cases. However in India hemochromatosis is a rare disease and only case reports are reported, as well the genetic mutation responsible for it is much less than western data. Non alcoholic steato hepatitis is the most common cause of these enzyme elevation after common causes are excluded. So next logical step is to order for USG Abdomen to document for fatty liver and markers of fatty liver like fasting blood glucose and fasting lipid profile. If there is concern about the possibility of chronic liver disease, tests to evaluate synthetic function of liver such as prothrombin time, S. Albumin with Albumin/Globulin ratio along with complete blood count including platelet count is recommended.

Step 3 – Uncommon causes and liver biopsy
Six months of life style changes with treatment of any identified cause is advocated. But if enzymes are persistently raised and worsening evaluation at an early date may be undertaken. The evaluation would be to rule out Auto immune hepatitis, Wilson’s disease (if age <40 yr) and hemochromatosis. Extra hepatic causes could be considered if clinical condition points towards it. Celiac disease is an important treatable condition in this respect. Similarly thyroid disorders can have deranged liver enzymes with persistant derangement and negative evaluation; liver biopsy may be indicated at 6 months.

References