INTRODUCTION

The last two decades have seen an enormous increase in the number of liver function test (LFT) being performed in healthy asymptomatic individuals. This is due to a number of factors such as the availability and convenience of automated biochemical tests, lower threshold for ordering blood tests by clinicians, increased health awareness in community leading to preventive health check-up and pre-employment check-ups. A significant number of liver function abnormalities are detected during such tests. About 4% of asymptomatic populations have elevated transaminase level. When faced with elevated transaminase in an asymptomatic individual, the clinician needs to address a number of issues such as:
1. Could the liver enzyme level be a laboratory error?
2. Is the level significantly and/ or persistently elevated?
3. If so, what is the likely cause?
4. How to plan further evaluation?
5. When to resort to costly or invasive investigations?

This chapter will focus on these issues in order to help the clinical decision making.

TRANSAMINASE (TRANSAMINASE)

Transaminase levels are sensitive indicator of liver cell injury and are helpful in recognizing hepatocellular diseases e.g. hepatitis. Aspartate transaminase (SGOT) is found in decreasing order of concentration in the liver, cardiac muscle, skeletal muscle, kidney, brain, pancreas, lungs, leucocytes and erythrocytes. Alanine transaminase (SGPT) is maximally concentrated in liver and is relatively more specific for the liver injury. Both enzymes are released into the body in increasing amounts when the liver cell membrane is damaged. Despite being a sensitive indicator of liver cell injury, the transaminase correlates poorly with severity of disease. It may be even be normal or mildly elevated in patients with advanced liver disease such as fibrosis or cirrhosis.

What is the normal level of transaminase is also a subject of debate. Conventionally, the normal range of transaminase in blood is about 30-40 U/L. However, the new recommendation for SGPT for males is <30U/L and for females <19U/L. This new range is 76.3% sensitive and 88.5% specific in detecting HCV viremia. The definition of persistent elevation is also debatable. Conventionally, chronic transaminasemia has been defined as persistent transaminase elevation for >6 months. However, practical considerations have redefined a period of 4 weeks as persistent elevation.

There is also no universal consensus on classification of degree of elevation, but a working definition is as follows:-
- Mild elevation < 3 times ULN
- Moderate elevation 3 - 20 times ULN
- Marked elevation > 20 times ULN

Transaminase level is elevated to some extent in all liver diseases. However, levels of more than 1000u/ml are present in only few conditions such as acute viral hepatitis, drug hepatotoxicity, toxic or ischemic hepatitis. Asymptomatic individuals usually have a mild to moderate elevation which can be due to most other liver diseases including chronic liver disease, cholestasis, hepatic tumors or fatty liver.
The different causes of transaminasemia in asymptomatic individuals is shown in Table I.

**EVIDENCE BASED CAUSES OF ASYMPTOMATIC TRANSAMINASEMIA**

In a study by Kundrotas et al only 0.5% of 19,877 healthy airforce trainees had elevated SGPT levels. A cause for elevation was found in less than 12% of these individuals of which two thirds were due to hepatitis B and C. On the other hand, in another study based on liver biopsy of 149 asymptomatic patients 56% had fatty liver, 20% had non A, non B hepatitis, 3% had hepatitis B, 11% had alcohol related changes, 8% had other causes and no cause was identified in 2% of patients. In a study conducted more recently 81 of 1124 patients with unexplained SGPT elevation underwent liver biopsy. 67 of these patients had evidence of steatosis and steato hepatitis, 4 had fibrosis, 2 had cirrhosis and 8 had normal histology. Berasain et al performed liver biopsies on 109 of 1075 patients with unexplained elevated SGPT, along with PCR for HBV-DNA and HCV-RNA. In this study 51.5% of these patients had chronic hepatitis, 32.7% patients had non specific changes and 15.8% patients had NASH. Thus, using more sophisticated techniques a large proportion of patients with elevated SGPT levels are found to have chronic viral infection. An Indian data among patients with elevated transaminases revealed that 30% had history of anti tubercular drug intake, 25% were chronic alcohol abusers, 25% had chronic hepatitis B or C and 10% had NASH. This data is derived from AIIMS which is a tertiary referral center and may be biased because of the referral pattern. However, an analysis of all available data suggests that the commonest causes for incidentally elevated transaminases are chronic viral hepatitis, usage of potentially hepatotoxic drugs, alcohol abuse and hepatic steatosis (NAFLD and NASH). Another important cause of elevated transaminase in our country is the use of indigenous drugs (Ayurvedic, Homeopathic, Unani, Herbal etc). There are a number of case reports and studies of such agents causing hepatotoxicity. More recently, there has been a surge of non alcoholic fatty liver disease associated with metabolic syndrome worldwide and this is rapidly becoming the commonest cause of asymptomatic transaminasemia.

**EVALUATION OF ASYMPTOMATIC PATIENTS WITH ELEVATED TRANSAMINASE**

Whenever an abnormal reading of transaminase is encountered in blood report of asymptomatic individual the first reaction should be to retest it. The decision of extensive evaluation should be clinically justified because it may be costly, anxiety provoking and risky (liver biopsy). The considerations before evaluation are to know about patients overall healthy status, any co-morbid condition (DM, Obesity, Dyslipidemia, etc), duration and pattern of enzyme elevation, history of alcohol intake, risk factors of viral hepatitis, drug history, family history of liver disease, socio economic status and all the risk of invasive procedure like liver biopsy.

The plan for investigation of elevated transaminase level, therefore, must be in accordance with the likely diagnostic possibilities. A meticulous history taking and clinical examination (for stigmata of CLD) is an essential modality at the very outset. Once the possibility of alcohol, drug, herb, diabetes, obesity or strenuous physical activity induced enzyme elevation has been excluded and a significant (>2-3 times of ULN) and persistent elevation (>2-4 weeks) established, then the serological markers for hepatitis B and C and an ultrasound examination of abdomen (for fatty liver or features of chronic liver disease) is indicated. A positive serological antibody test for hepatitis C should be confirmed by HCV RNA test by PCR method which is currently the gold standard for detecting hepatitis C infection. An assessment of the severity of liver damage by liver biopsy may be indicated in genotype 1 and 4 prior to treatment. Hepatitis B infection is tested by hepatitis B surface antigen. A positive test along with a positive core antibody IgM indicates a recent infection whilst a positive core antibody IgG indicates chronicity. Once HBV infection is established, the next step is to determine whether the virus is replicative or non replicative. A positive HBsAg or HBV DNA is indicative of a replicative virus infection that should be treated depending on the viral load.

In patients with negative viral serological markers, the ultrasound examination is useful for evidence of steatosis. If there is evidence of steatosis, then a clear distinction has

<table>
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<tr>
<th>Common Causes</th>
<th>Uncommon Causes</th>
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<tr>
<td>NAFLD</td>
<td>Wilson’s disease</td>
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<tr>
<td>Alcoholic liver disease</td>
<td>Hemochromatosis</td>
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<tr>
<td>Chronic viral hepatitis</td>
<td>Alpha-1 - AT deficiency</td>
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<td>Medication</td>
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<tr>
<td>Autoimmune hepatitis</td>
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<td>Celiac disease</td>
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Table I. Causes of Asymptomatic Elevation of Transaminases
to be made between alcohols induced steatosis and NAFLD. The diagnosis of alcohol abuse is supported by finding a SGOT: SGPT ratio of at > 2:1 along with macrocytosis in an individual with history of alcohol abuse. In contrast to patients with alcohol-related liver disease, patients with non-alcoholic steatosis usually have a normal or mildly elevated SGOT: SGPT ratio that is less than 1.5 : 1. An ultrasound elastography may be a useful non-invasive method for assessment of fibrosis but the diagnosis of NASH requires a liver biopsy to demonstrate inflammation / necrosis +/- fibrosis in addition to fatty infiltration. NAFLD and NASH have different natural history. Whilst NAFLD has a relatively benign course, patients with nonalcoholic steatohepatitis can progress to cirrhosis, hence the differentiation is important. Further assessment of patients with steatosis requires a lipid profile, blood sugar testing and thyroid function test. Treatment modalities will need to address any abnormalities in these tests.

Patients without evidence of drug induced elevation, viral infection and steatosis should undergo further investigations for possibility of Auto-immune hepatitis, Wilsons disease, Haemochromatosis and Coeliac disease in which approximately 20% patients have abnormal enzymes. A screening programme in this group of patients may include a serum protein electrophoresis, ANA, ASMA, Se. Ceruloplasmin level, Se. Iron/TIBC and anti-endomysial antibody/ anti tTG lg A levels. Elevated SGOT levels may be caused by extra hepatic disorders with the commonest being striated muscle disorders. If striated muscle is the source of elevation, then serum level of Creatine Kinase and Aldolase should also be elevated. Thus, the level of these enzymes should also be measured if hepatic conditions have been ruled out.

Despite the comprehensive testing as described above, the cause of elevation of the transaminase level may remain unidentified in some patients. A liver biopsy should ideally be done in all such patients. However, there is some evidence that close clinical follow-up is the most cost effective strategy in these patients. In support of this strategy is a study which showed that liver biopsy led to a change of treatment in only 2 of 36 patients with unexplained elevated transaminase. It has been suggested that if transaminase levels are less than twice the ULN and no chronic liver disease has been identified, then regular clinical follow up may suffice. On the other hand, if the transaminase level is persistently more than twice the ULN, then a liver biopsy should be considered. Although the result of the biopsy is unlikely to change the diagnosis or management, it would at least provide reassurance to the patient and the clinician that no serious disorder is present.

An algorithm for investigating patients with asymptomatic elevated SGOT/SGPT is provided in Fig.1.

### Table II. Stepwise Evaluation of Isolated (or Predominant) Mild Elevation of SGOT

1. Repeat and confirm the abnormality
   - if resolved, no further evaluation; recheck in 3-12 months
2. Confirm hepatic origin by measuring SGPT and CPK
   - if SGPT normal and CPK elevated, evaluate for heart or muscle disease
3. Perform history and physical examination
   - If drug-induced or alcoholic liver disease suspected, repeat test(s) 2-8 weeks after drug withdrawal or alcohol abstinence.
   - if specific diagnosis suspected, obtain appropriate disease-specific marker
   - if no diagnosis suspected, obtain all disease-specific markers
   - if fatty liver suspected and all disease-specific markers negative or normal, follow serial liver test(s) during period of dieting
   - if test(s) normalize with weight loss, presume fatty liver
4. Consider hepatic imaging test (US or CT) to exclude other disease and / or confirm fatty liver (low CT attenuation value)
5. Consider liver biopsy when test(s) abnormality persists longer than 6 months and diagnosis uncertain
Fig. 1: Algorithm for Diagnosis of Elevated Transaminase in Asymptomatic Individual

Elevated SGPT
In at least 2 determinations
2-4 wks apart

History
Previous liver disease, risk factors
Drugs, alcohol use
Family history, associated co-morbid conditions

Physical examination
Chronic liver disease stigmata
Other systemic disease evidence

Frequent causes of chronic disease

Chronic viral hepatitis
Risk factors, anti-HCV, HbsAg, anti-HBs, anti-HBc
Imaging (USG)

Alcoholic liver disease
History taking, GOT: GPT ratio>2
Macrocytosis
Imaging (USG)

Non-Alcoholic fatty liver
Predisposing factors
Alcohol exclusion
Imaging (USG)

Autoimmune hepatitis
Autoantibodies: ANA, ASM, Anti-LKM, anti-LCI, anti SLA, Anti-LP, Hypergammaglobulinemia

Non-frequent causes of chronic liver disease

Hemochromatosis
TSI, ferritin, genetic study

Wilson's disease
Ceruloplasmin, Kayser-Fleischer ring cupriuria

Alfa 1-AT deficiency
A1 AT determination, Proteinogram, Phenotype

Alcoholic liver disease
History taking, GOT: GPT ratio>2
Macrocytosis
Imaging (USG)

Non-Alcoholic fatty liver
Predisposing factors
Alcohol exclusion
Imaging (USG)

Autoimmune hepatitis
Autoantibodies: ANA, ASM, Anti-LKM, anti-LCI, anti SLA, Anti-LP, Hypergammaglobulinemia

Frequent causes of non-liver involvement

Myopathies
CPK, aldolase

Celiac disease
Antiendomysial, Anti-transglutaminase, antibodies

Thyroid disease
T3, T4, TSH

Prophyrias
Physical examination, porphyrins

Liver biopsy