Chapter

67

Asymptomatic Patients with Raised Enzymes: What to do?

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INTRODUCTION

Hepatic transaminase tests such as alanine transaminase (ALT) and asparate transaminase (AST) are often part of standard laboratory panels in asymptomatic out patients, similar to screening tests for blood donors and for life insurance applicants. The evaluation of an abnormal ALT or AST levels in an asymptomatic patient is a common challenge encountered by primary care physicians.

> Up to 4% of asymptomatic population may have elevated serum liver chemistries

According to American Gastroenterological Association (AGA), 1-4% of asymptomatic population may have elevated serum liver chemistries[1]. Given the frequency of this problem, physician should develop an informed approach to the investigation of transaminase elevation. Since chronic liver diseases are characterized by long preclinical phase, so early detection of significant liver disease allows therapeutic intervention and life style changes aiming at regression of liver fibrosis.

MARKERS OF HEPATIC INJURY AND NECROSIS

ALT and AST are two most reliable markers of hepatocellular injury or necrosis. Of the two, ALT is thought to be more specific (83%) than AST (70%)[2] for hepatic injury because it is present mainly in cystosol of the liver and is low concentrations elsewhere. AST has cytosolic (20%) and mitochondrial forms (80%) and is present in tissues of liver, heart, skeletal muscles, kidneys, brain, pancreas and lungs and in white and red blood cells[3].

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The ratio of AST to ALT has some clinical utility, but has important limitations. AST/ALT ratio greater than 2 characteristically present in alcoholic hepatitis, due to alcohol related deficiency of pyridoxal 5' phosphatage (B6)[4] and AST/ ALT ratio > 1 observed in 61% of patients with advanced fibrosis. In contrast patients with non-alcoholic fatty liver Disease (NAFLD) the AST/ALT ratio is less than 1[5]. Wilson disease can cause the AST/ALT ratio to exceed 4[6].

The AGA review states that serum ALT has diurnal variations, may vary day to day and may be affected by exercise. It also notes that serum AST may be 15% higher in black men than white men[1]. The magnitude of transaminase alteration can be classified as mild (< 5 times of upper reference limit) or moderate (> 5-10 times) or marked (> 10 times). Pattern of AST, ALT values is given in Fig. 1, while etiology of ALT and AST elevation is shown in Table 1.

Table 1: Etiology of ALT/AST elevations

Common hepatic causes	*Less common hepatic causes*	*Nonhepatic causes*
Alcohol	Autoimmune hepatitis	Celiac disease
Cirrhosis	Hemochromatosis	Hemolysis
Hepatitis B (chronic)	Alpha 1 – antitrypsin deficiency	Myopathy Hepatitis
C (chronic)	Wilson's disease	Hyperthyroidism
Steatosis/Steato-hepatitis		Strenuous exercise
Medications/ toxins		Macro-AST
Acute viral hepatitis		

Any confirmed (tested twice) significant rise (> 1.5 to 2 time of normal reference range) in transaminase activity (especially ALT) warrants additional investigations for detection of underlying liver disease. A good clinical history and physical examination is the

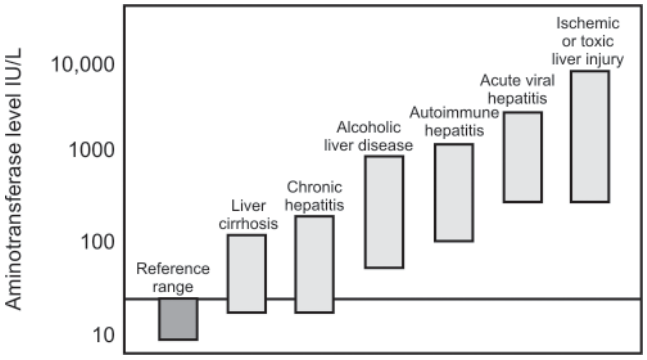

Fig. 1: Serum aminotransferase levels in various liver diseases. Patients with acute viral or ischemic or toxic liver injury reach the highest aminotransferase levels, but there is a broad overlap in aminotransferase values between patients with acute alcoholic hepatitis and autoimmune hepatitis as well as between patients with chronic hepatitis and liver cirrhosis. Both chronic hepatitis and cirrhotic patients may have aminotransferase levels within the reference range. The line indicates the upper limit of the reference range

cornerstone of the evaluation of patient with mildly elevated enzymes[1]. The history should attempt to identify risk factors like intake of alcohol, medications, and herbal supplement, drug use, blood product transfusion and symptoms of liver disease. Table 2 lists selected medications and herbal supplements that may cause elevated transaminase levels. Physicians should ask patients directly about their use of illicit drugs, herbal supplement, and other alternative supplements because they are sometime omitted from the patient's initial response to questions[7-9]. Acetaminophen induced hepatic damage causes 54 and 16% of cases of acute liver failure in UK and USA respectively[10].

Table 2: Common agents that can cause liver transaminase elevations

Medications	*Herbal supplements/vitamins*
Acetaminophen	Chaparral leaf
Amiodarone (Cordarone)	Ephedra
Amoxicillin – clavianic acid	Gentian
Carbamazepine (Tegretol)	Germander
Fluconazole (Diflucan)	Jin bu huan
Glyburide (Micronase)	Kava
Heparin	Scutellaria (skullcap)
Isoniazid (INH)	Senna
Ketoconazole (Nizoral)	Shark cartilage
Labetalol (Normodyne)	Vitamin A
Nitrofurantoin (Furadantin)	
Nonsteroidal anti-inflammatory drugs	
Phenytoin (Dilantin)	
Protease inhibitors	
Sulfonamides	
Trazodone (Desyrel)	

As detailed in Table 1 many non-hepatic diseases can cause transaminase elevations: examples are, diabetes, obesity, heart disease, thyroid disease, muscles disease etc. Physical finding and sequelae of liver dysfunction are given in Table 3.

INITIAL LABORATORY EVALUATION

Despite the emergence of widespread vaccination, hepatitis 'B' remains a common cause of chronic liver disease in adults. All patients presenting with mild increase in transaminase levels, testing for HCV antibodies and HBsAg is advisable. In subjects who are seropositive for hepatitis 'B' further marker's are needed depending upon clinical situation (e-minus Vs wild type). If patient tests positive for HCV antibodies, then quantitative HCV RNA testing follows. It is important to emphasize that degree of transaminase alteration is a poor guide for severity of disease in patients with established chronic viral hepatitis, unless an AST / ALT ratio greater than 1 is found, suggestive of presence of cirrhosis[11-14]. In patients with viral hepatitis liver biopsy is needed to assess progression, evaluate the need for therapy and to establish prognosis. Prothrombin time (PT) and serum albumin should be ordered to identify patients with abnormality of protein synthesis, neutropenia or thrombocytopenia can, alongwith an elevated PT suggest advanced liver disease.

LIFESTYLE MODIFICATION, FOLLOW-UP AND IMAGING

Effective lifestyle modifications include complete abstinence from alcohol, control of diabetes and hyperlipidemia, weight loss in overweight patients and stopping or changing potentially hepatotoxic medications and supplements. A repeat set of liver chemistries should be obtained after 6 month (interval depend case to case); if abnormalities persist, then further evaluation is needed, by imaging like ultrasonography and computed tomography.

> Patients with impaired hepatic synthetic function (PT and albumin) should have a more-accelerated evaluation of their abnormal transaminases.

Steatohepatitis or non-alcoholic fatty liver disease (NAFLD) often is discovered by imaging. This condition may be the most frequent cause of mild liver chemistry elevations and according to National Health and Nutritional survey[15], point prevalence is about 23%

Table 3: Clues in the evaluation of mildly elevated liver transaminase levels

Clinical clue	*Suggested diagnosis*
Longstanding alcohol abuse	Cirrhosis
Intravenous drug use, history of blood product transfusions, nonsterile needle exposure	Hepatitis B or C
Obesity, diabetes, hyperlipidemia, AST/ALT ratio < 1.0	Steatosis/steatohepatitis
AST/ALT ratio > 2.0	Alcoholic liver disease, Wilson's disease
Increased iron levels	Hemochromatosis
Polypharmacy, illicit drug use, or certain herbal supplement use	Substance/ medication-induced
Frequent, strenuous exercise	Exercise-induced
Intestinal bloating; oily bulky stools	Celiac sprue
Hepergammaglobulinemia	Autoimmune hepatitis
Reduced ceruloplasmin levels, Kayser-Fleischer ring	Wilson's disease
Depressed thyroid-stimulating hormone levels	Hyperthyroidism

among American adults. Suspicion of NAFLD is increased by the presence of conditions linked to the metabolic syndromes and insulin resistance (increased body mass index, diabetes, hyperlipemia) although disease may occur in patients without these associated factors[15,16]. The diagnostic approach to suspected NAFLD is aimed at ruling out other causes of liver disease since there is no specific blood test for diagnosis. Distinguishing between simple steatosis with or without minimal inflammation and associated fibrosis is not possible on clinical ground alone, and therefore liver biopsy should be performed in order to confirm diagnosis and assess prognosis[15-18].

Presence of a mild elevation in aminotransaminase level in female patients with concomitant autoimmune disorder (e.g. autoimmune thyroiditis, connective tissue disease) is suggestive of autoimmune hepatitis. 80% of patients may have hypergammaglobulinemia even in the absence of liver cirrhosis[19,20]. Auto antibodies (antinuclear, anti-smooth muscle and anti-liver kidney microsomes) should be tested, although the criteria for diagnosis are complex and include liver biopsy. Patient may have dramatic response to corticosteriods[19-21].

Wilson's disease (homozygote frequency 1:30000-1:300000) should be suspected in young patients with signs of hemolysis or concomitant psychiatric or neurologic symptoms, and serum ceruloplasmin levels and copper metabolism (serum and 24 hour urinary copper) should be tested. Diagnosis can be confirmed by slit-lamp examination for Kayser-Fleischer rings, although liver biopsy with quantitative copper measurement may be needed where no clear clinical diagnosis is possible[22, 23].

Although α-1 antitrypsin deficiency is not a rare disease, affecting 1:1600-1:2800 newborns in Europe and the United States, it is an unusual cause of transaminase alteration among adults since the disease is usually identified in childhood[24]. It can be suspected in adult patients with concomitant pulmonary disease (emphysema), although low serum α-1 antitrypsin levels and phenotype determination provide definite diagnosis[24].

HFE-related hereditary hemochromatosis is a fairly common autosomal recessive condition (homozygote frequency 1:200-1:400). High ferritin levels and, most importantly, a transferrin saturation index greater than 45% are strongly suggestive of the disease[25]. The presence of diabetes, heart disease or arthritis is also suggestive, and mutation analysis of the HFE gene may confirm the diagnosis, especially if the patient is of northern European descent[26].

Up to 10% of patients with unexplained hypertransaminasemia actually have celiac disease, and minimal or mild alteration of transaminase levels may be the only visible part of the "celiac iceberg"[27]. In these patients, screening by measuring tissue transglutaminase antibodies and confirmation and grading of the disease by small bowel biopsy are required for diagnosis[28].

The results of these studies suggests that a liver biopsy in not mandatory in asymptomatic patients with an unexplained rise in AST or ALT. According to the AGA the decision to perform a liver biopsy need to be

made on individual basis, taking into consideration the patient's age, lifestyle, liver chemistry abnormalites, desire for prognostic information and associated co-morbid conditions[1].

There is controversy concerning the need for evaluation of people with slightly increased transaminase activity, but still within the normal range. 16% of patients with chronic hepatitis 'C' infection and 13% of patients with NAFLD have varying degrees of histological damage despite showing persistently normal transaminase levels[17,29]. Italian retrospective cohort study in 6835 first-time blood donors suggested that normal values of ALT were based on a reference population which possibly included patients with subclinical hepatitis 'C' infection and NAFLD[30]. According to the authors, lowering of the upper limit of normal (ULN) for ALT is advisable in patients with chronic HCV infection or NAFLD. The study and conclusions were criticized by others[31], because lowering the ULN of ALT would create an overwhelming number of false-positive results. However, a recent Korean study showed a positive association between high normal serum ALT (35-40 IU/L) levels and mortality from liver disease, even after adjustment for alcohol consumption, obesity, plasma glucose and serum lipids[32]. It may therefore be justified to lower the ULN for ALT in populations with a high prevalence of liver diseases.

CONCLUSION

Alterations in liver enzymes levels are one of the most common problems encountered in every day clinical practice. Following the simple algorithm detailed

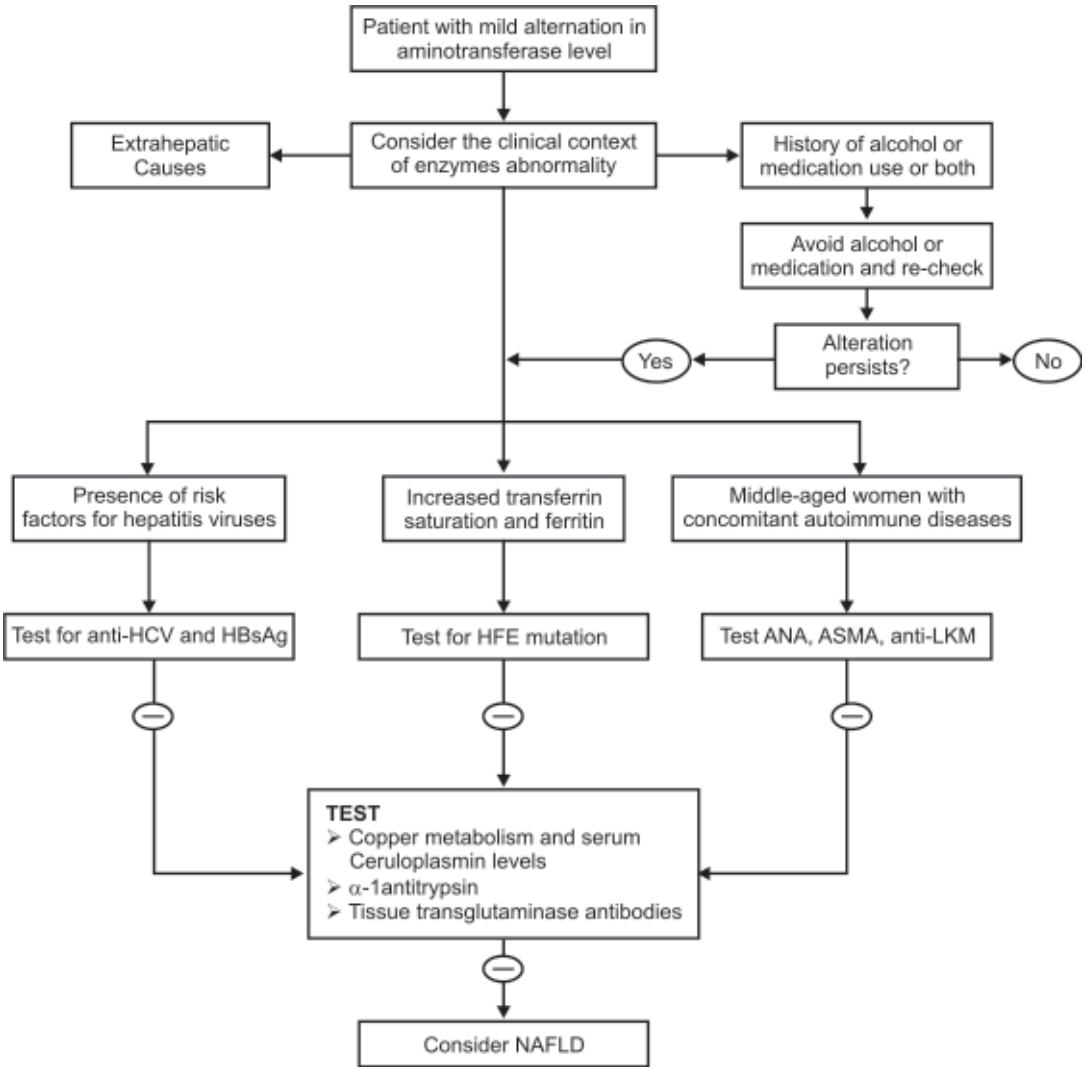

Fig. 2: Schematic, initial diagnostic algorithm for a patient presenting with mild aminotransferase abnormality. HCV = hepatitis C virus, HBsAG = hepatitis B surface antigen, ANA = antinuclear antibodies, ASMA = anti-smooth muscle antibodies, LKM = liver kidney microsomes

in Fig. 2 it is possible in most cases to identify the cause of abnormal liver function test. Awareness of the prevalence of determined liver disease in specific populations and of possible hepatic involvement during systemic illness or drug therapies may help the clinician to identify the cause of alterations efficiently. In some cases, however, we cannot establish a diagnosis at first presentation. It may then be best to follow a "watch and wait strategy" provided that the clinical presentation does not mandate therapy.

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