

Evaluation of Increased Serum Aminotransferase Level in Asymptomatic Patient

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ABSTRACT

Liver test abnormalities are commonly found in ambulatory patients. The liver function tests are routinely included in chemistry panels. According to the American Gastroenterological Association (AGA), 1-4% of the asymptomatic population may have elevated serum liver chemistry. The majority of asymptomatic patients with liver test abnormalities have no evidence of liver disease. Unfortunately, abnormal results for liver function are often not adequately investigated, missing an important chance of identifying treatable chronic liver disease. Potential causes of liver aminotransferase elevation are originated from hepatic causes (viral hepatitis, alcohol use, medication use, steatosis and non-alcoholic steatohepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, α -antitrypsin deficiency) and non hepatic causes. In the majority patients (92%) with chronically elevated aminotransferase tests, etiologies of the liver disease could be diagnosed through close clinical approach, which includes: history taking, physical examination, and blood tests. If elevation persists after an appropriate period of observation, further testing may include ultrasonography and other serum studies. In about 8% of patients with chronic abnormal alanine aminotransferase levels no cause is found. So, if liver test abnormalities cannot be explained by other findings, liver biopsy examination can help to exclude serious liver disease or disclose the nature and severity of liver disease.

Keywords: *elevated liver transaminase, asymptomatic patients, chronic liver disease*

ABSTRAK

Gangguan tes fungsi hati cukup sering dijumpai pada pasien rawat jalan. Berdasarkan the American Gastroenterological Association (AGA), 1-4% dari populasi yang tidak mengalami keluhan mengalami peningkatan enzim hati. Mayoritas dari pasien tersebut ternyata terbukti tidak menderita penyakit hati. Namun gangguan fungsi hati yang terjadi sering tidak diinvestigasi secara memadai, sehingga penyakit hati kronis yang bersifat dapat disembuhkan tidak dapat teridentifikasi. Penyebab peningkatan aminotransferase dapat berasal dari virus hepatitis, alkohol, obat-obatan, steatosis dan non alkoholik steatohepatitis, hepatitis autoimun, hemokromatosis, penyakit Wilson, dan defisiensi α -antitripsin. Melalui pendekatan klinis yang tepat, 92% pasien yang mengalami peningkatan aminotransferase kronis dapat diketahui etiologinya, melalui anamnesis, pemeriksaan fisik dan laboratorium. Apabila kadar aminotransferase masih meningkat diperlukan pemeriksaan ultrasonografi dan pemeriksaan laboratorium lainnya. Sedangkan sejumlah 8% pasien dengan peningkatan kronis aminotransferase tidak diketahui penyebabnya. Apabila penyebab peningkatan aminotrasferase masih belum ditemukan maka diperlukan pemeriksaan biopsi hati untuk menyingkirkan adanya penyakit hati yang serius.

Kata kunci: *peningkatan enzim hati transaminase, pasien tanpa gejala, penyakit hati kronis*

INTRODUCTION

Normal laboratory values are defined as the mean of the distribution \pm 2 standard deviations of the normal population. Therefore, by definition, 5% of normal patients will have abnormalities of any given test (2.5%

are above and 2.5% are below 2 standard deviation). Normal laboratory values may vary according to age, sex, blood group, and postprandial state as well as other factors. If the result of laboratory values is normal or slightly increase, it does not ensure that the patient is

free from the disease.¹ Liver disease is often reflected by abnormal results of at least one of the liver function test (serum liver enzymes). These serum liver enzymes are commonly referred to liver function tests, though they actually reflect hepatocyte integrity or presence of cholestasis rather than liver function.²

In 1989, a panel of 12 European and American experts by consensus defined liver injury as an increase of more than twice the upper limit of the normal range of alanine aminotransferase (ALT) or conjugated bilirubin, or a combined increase of aspartate transaminase (AST), alkaline phosphatase (ALP), and total bilirubin.³ Isolated alterations of biochemical markers of liver damage in seemingly healthy patient can present a challenge for the clinician. Mild elevation in liver chemistry tests, such as ALT and AST can reveal serious underlying disease or have transient and benign etiologies. These liver chemistry tests often are part of standard laboratory panels in asymptomatic outpatients, similar to screening test for blood donors and for life insurance applicants.²

According to the American Gastroenterological Association (AGA), 1-4% of the asymptomatic population may have elevated serum liver chemistry.¹ Kundrotas et al, conducted a study in a population of asymptomatic US Air Force basis trainee blood donors. Of 44,160 individuals screened, 19,877 (45%) voluntarily donated blood, 99 (0.5%) of which had confirmed ALT elevation (ALT > 2.25 standard deviation or ALT > 55 IU/L). Abnormal results for liver function are often not adequately investigated, missing an important chance of identifying treatable chronic liver disease.⁴ Sherwood et al, underwent a study to determine whether abnormal results for liver function test were investigated in primary care and findings on full investigation. Of 8,208 tests for liver function requested by doctors in the six months period, they identified 873 patients with abnormal results (γ -glutamyltransferase, alkaline phosphatase and ALT concentrations at least twice the upper limit of the reference range). Of 873 patients, 157 (18%) were not appropriately followed up. With the reason, this article reviews the interpretation and how to manage an asymptomatic patient with mild elevation of liver aminotransferase levels.⁵

AMINOTRANSFERASE ENZYME

Aminotransferases (ALT and AST) constitute a group of enzymes that catalyze the interconversion of amino acids and alpha-oxoacids by transfer of amino groups. These enzymes have been suggested as enzymes of greatest clinical significance.

Aspartate aminotransferase (AST) is one of the most active enzymes in the cell, which exists in mitochondrial and cytosolic variants, and the detailed iso-enzyme pattern is tissue-specific. Besides in liver cells, AST is also abundantly expressed in several non hepatic tissues including heart, skeletal muscle, and blood, kidney, pancreas, spleen, lung and erythrocytes. AST escapes in large amounts from dead or dying tissues and enters the bloodstream. Therefore, it is often measured in blood samples for medical diagnostic purpose and evaluation of liver and heart disease.

Alanine aminotransferase (ALT) exists in mitochondrial and cytosolic variants. The detailed iso-enzyme pattern is tissue-specific. High concentrations of ALT are found in the liver, and relatively low concentrations are found in the heart, muscle and kidney. So it is frequently considered specific for hepatocellular injury. It escapes in large amounts from dead or dying tissues and ALT may be measured in blood samples for medical diagnostic purposes and to monitor the course of treatment for hepatitis. Injury to the liver, whether acute or chronic, eventually results in an increase in serum concentrations of aminotransferases. Increased serum levels of ALT and AST indicate hepatocyte injury and necrosis. The increase of absolute level of these aminotransferases (enzymes) in serum does not correlate with the extent of the hepatocellular injury and is neither specific for the cause of liver disease nor predictive of outcome.^{2,6}

There are four major types of liver injury: hepatocellular, autoimmune, cholestasis and infiltrative. The predominant laboratory abnormality defines the pattern of injury. A hepatocellular pattern is marked by isolated or predominant elevations of serum transaminase. Cholestasis and infiltrative patterns, in contrast, have elevation in serum alkaline phosphatase with normal or mild elevations in serum aminotransferase. An autoimmune mechanism can present with either a hepatocellular pattern if hepatocytes are involved (autoimmune hepatitis) or cholestasis if the immune mechanism targets the biliary ducts (e.g. primary biliary cirrhosis).⁷

The measurement of serum aminotransferase levels has been in clinical practice for 50 years, and the normal values have not changed. However, recent studies from Italy, Sweden, and France have shown that increased ALT levels not only indicate hepatocellular damage, but also correlate independently with sex, body mass index (BMI), and abnormal lipid and carbohydrate metabolism, and strenuous exercise.^{2,7,8}

Serum ALT activity, the variable most commonly measured to assess hepatic disease, fails to identify many patients with hepatic injury. Prati et al, proposed to revise the upper limit of normal value for ALT to improve the sensitivity of this test in identifying subclinical liver disease.⁹ Current upper limit for ALT is 30 U/L for female and 40 U/L for male. This study redefined ALT limits in blood donors at low risk for non-alcoholic fatty liver disease (NAFLD) and without hepatitis B or C to 19 U/L for female and 30 U/L for male. When applied to 209 anti HCV positive donors, the new thresholds had 76.3% sensitivity and 88.5% specificity in identifying patients with hepatitis C viremia compared with 55% and 97.4% for previous thresholds.

The magnitude of aminotransferase alteration can be classified as mild, moderate and very high.^{2,6} Very high aminotransferase enzyme (> 15-fold the upper normal limit) are typically seen in acute viral hepatitis, toxin or drugs induced liver damage, ischemic hepatitis, hepatic artery ligation and fulminant Wilson's disease. Moderate increase of aminotransferase (5-10-fold) can be seen in many form of acute and chronic liver disease, including viral and autoimmune hepatitis, alcoholic hepatitis, and hepatic injury caused by metabolic diseases, such as hemochromatosis or Wilson's disease. Mild increase (< 5-fold) aminotransferase levels can be seen in many causes (Table 1).

Table 1. Causes of mild increases in ALT and AST levels^{10,11}

Causes	Diseases	Work up
Hepatic causes	Alcohol abuse	ALT/AST ratio > 2.0
	Medications	None
	Chronic hepatitis B	HBsAg, HBeAg, HBV DNA
	Chronic hepatitis C	Anti HCV, HCV RNA
	Steatosis and non-alcoholic steatosis hepatitis	Biopsy
	Autoimmune hepatitis	Serum protein electrophoresis Antinuclear antibody Anti-smooth muscle antibody
	Hemochromatosis	Transferrin saturation 45% HFE gene analysis for C282Y mutation
Nonhepatic causes	Wilson's disease	Genetic analysis Low serum copper, high urine copper Kayser-Fleischer ring
	α -antitrypsin deficiency	A1AT phenotyping
	Celiac sprue	Antiendomysial and antigliadin antibodies
	Inherited disorders of muscle metabolism	
	Acquired muscle disease	Creatinine kinase/aldolase level
	Strenuous exercise	

ALT: alanine aminotransferase; AST: aspartate transaminase; HBsAg: hepatitis B surface antigen; HBeAg: hepatitis B e-antigen; HCV: hepatitis C virus; DNA: deoxyribonucleic acid; RNA: ribonucleic acid

It is not always possible to distinguish acute from chronic hepatic injury according to the aminotransferase levels. Although chronic hepatic injury is defined pathologically, patients with abnormal liver function test ALT for > 6 months are considered to have chronic hepatic injury. Most patients with chronic hepatitis C (the most common form of chronic hepatic injury) have ALT values one to four times the upper reference limit and 90% have maximum ALT less than seven times the upper reference limit. The best values for recognizing acute hepatic injury were 200 U/L for AST with sensitivity of 91% and specificity of 95%, while 300 U/L for ALT with sensitivity of 96% and specificity of 94%.¹⁰

ETIOLOGY OF MILD AMINOTRANSFERASE ELEVATION

The most common etiologies for chronic liver amonitranferase levels are alcohol use, non-alcoholic fatty liver disease, viral hepatitis, and other rare etiologies (autoimmune hepatitis, hereditary liver diseases).^{5,11,12} Chronic hepatitis C was diagnosed in 15.3% of patients, alcoholic liver disease in 8%, autoimmune hepatitis, primary billiary cirrhosis in 1.3% each, α -1 antitrypsin deficiency in 0.7%, and non-alcoholic steatohepatitis and or steatosis in 42%, and 36 (24%) patients had chronic hepatitis of unknown origin.¹³ The cause of an elevated alanine amonitranferase levels may be divided into hepatic causes and nonhepatic causes (Table 1).

NON-ALCOHOLIC FATTY LIVER DISEASE

There are 2 histologic patterns of non-alcoholic fatty liver disease (NAFLD): non-alcoholic fatty liver and non-alcoholic steatohepatitis (NASH). NAFLD is the most common cause for unexplained persistent elevation of ALT level once hepatitis C and other known causes of chronic liver disease have been excluded. Most patients with NAFLD in cross sectional studies are asymptomatic. Obesity is the most common abnormality on physical examination and is present in 30-100% patients. Most patients with NASH (50-90%) have abnormal aminotransferase activities. The degree of enzyme elevation is between 1 and 4 times the upper limit of normal values. There is no accurate noninvasive method to diagnose NASH. There are four sonographic findings of diffuse fatty change in the liver: (1) a diffuse hyperechoic echostructure (bright liver), (2) increased liver echostructure compared with kidney, (3) vascular blurring, (4) deep attenuation. In a small retrospective study,

a combination of these parameter allowed diagnosis of fatty liver with sensitivity of 83% and specificity of 100%.^{14,15} The gold standard for diagnosing NAFLD is clinico-pathological correlation, with confirmation of steatosis by liver biopsy and exclusion of other causes (e.g. alcohol).¹⁶

Drug-related Hepatotoxicity

It is important to recognize the pattern of liver injury, since certain drugs tend to create injury predominantly according to one pattern or the other, these include: (1) hepatocellular (e.g. amiodarone, acetaminophen, allopurinol, isoniazid, statin, rifampicin, etc), with elevated ALT predominantly; (2) cholestatic (e.g. amoxicillin-clavulanic acid, chlorpromazine, clopidogrel, irbesartan, etc), with elevated ALP and total bilirubin predominantly; (3) mixed (e.g. amitriptyline, captopril, clindamycin, enalapril, verapamil, etc) with elevated ALP and ALT predominantly. In most cases, there is no effective treatment other than stopping the drug and providing general supportive care. Prompt use of N-acetylcysteine after acetaminophen overdose and intravenous carnitine for valproate-induced mitochondrial injury are exceptions.³

Chronic Viral Hepatitis

In chronic hepatitis B, AST and ALT may return to normal despite persistence of infection. Liver biopsy and treatment should be considered in patients with positive test for hepatitis virus, DNA and hepatitis B e antigen. The natural history of hepatitis C is quite variable. In acute HCV infection elevation in serum ALT levels occurs approximately 2-8 weeks after exposure. Although the definition of chronic hepatic injury by increased ALT is widely accepted, 15-50% patients with chronic hepatitis C have persistently normal ALT. Nafees et al, conducted a study to find out how many subjects with asymptomatic HCV infection have normal or elevated serum AST and ALT levels. They revealed that 90.76% and 87.45% of patients had elevated AST and ALT respectively.¹⁷ The majority of patients with persistent normal ALT had histologic evidence of chronic hepatitis on biopsy but, in general, had milder inflammation, less fibrosis, and lower rates of progression to cirrhosis than HCV patients with increased ALT. Patients infected with HCV genotypes 2 and 3 had sustained virological response rates over 80%, after treated by daily ribavirin and peg-IFN- α .^{18,19}

Therefore, it arises a question: should all patients with abnormal liver function tests in primary care be tested for chronic viral hepatitis? David et al, recommended that all patients should undergo viral test where a clear clinical indication of infection is

present (e.g evidence of intravenous drug use) or all patients who originated from countries where viral hepatitis is prevalent.²⁰

Autoimmune Hepatitis

The presentation of autoimmune hepatitis is heterogeneous, and the clinical course may be characterized by periods of decreased or increased activity; thus, clinical manifestations are variable. The spectrum of presentation ranges from no symptoms to debilitating symptoms and even fulminant hepatic failure. The laboratory abnormalities in general, aminotransferase elevations are more striking than abnormalities in bilirubin and alkaline phosphatase levels. A useful screening test is serum protein electrophoresis (more than 80% patients have hypergammaglobulinemia). Additional test that are commonly ordered include serologic test for antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), and liver-kidney microsomal antibodies. Furthermore, a liver biopsy is essential to confirm the diagnosis.^{21,22}

Type 2 Diabetes

Individuals with type 2 diabetes have a higher incidence of liver function test abnormalities than individuals who do not have diabetes. The most common abnormality is elevated ALT. Mild chronic elevation of aminotransferase often reflects underlying insulin resistance. Any diabetic patient found to have a mild chronic elevation of ALT, or elevation of ALT < 250 U/L for > 6 months should be screened for treatable causes of chronic liver disease, particularly hepatitis B, or C, and hemochromatosis, there is increased incidence of the diseases in type 2 diabetes. Elevation of aminotransferase within three times the upper limit of normal values is not a contraindication for starting oral diabetic or lipid modifying therapy. In contrast, antidiabetic agents have generally been shown to decrease ALT levels as tighter blood glucose levels are achieved.²³

Alcohol Use

The diagnosis of alcohol abuse can be difficult because many patients conceal information about their alcohol use. This diagnosis is supported by the finding of ratio of AST to ALT > 2 : 1. In a study of a hundreds of patients who had histologically confirmed liver disorders, more than 90% of patients who had ratio AST to ALT > 2 : 1, had alcoholic liver disease. The increase ratio reflects primary the low serum activity of ALT in patients with alcoholic liver disease. This decrease is due to an alcohol-related deficiency of pyridoxal 5-phosphatase. Measurement of γ -glutamyl-transferase may also be helpful in diagnosing alcohol use.²¹

Other Causes

Hereditary hemochromatosis, Wilson's disease and α -antitrypsin deficiency are sometimes detected in clinical practice. Hereditary hemochromatosis is a common genetic disorder. Cost effective screening starts with the measurement of serum iron and total binding capacity. A transferrin-saturation value $> 45\%$ is suggestive of hemochromatosis. A liver biopsy should be performed in assessing hepatic iron and the severity of liver damage. Wilson's disease, a genetic disorder of biliary copper excretion, may cause elevated aminotransferase levels in patients with no other symptom of the disease. In Wilson's disease, serum ceruloplasmin will be reduced in approximately 85 % of affected patients. In 24-hour urine collection, excretion of more than 100 μg of copper/day is suggestive of Wilson's disease. The diagnosis is usually confirmed by liver biopsy to measure hepatic copper levels. α -antitrypsin deficiency is an uncommon cause of chronic liver disease. Decreased level of α -antitrypsin can be detected either by direct measurement of serum levels or by the lack of a peak in α -globulin bands on serum protein electrophoresis. The best diagnosis is established by phenotype determination.^{10,21} Occult coeliac sprue is recognized as a cause of raised aminotransferases. Antiendomysial and antigliadin antibodies are useful confirmatory tests.²⁴ Elevated serum aminotransferase levels, especially AST levels, may be caused by disorders that affect organs or tissues other than the liver, with the most common affected organ being the striated muscle. Conditions or activities that can cause such elevations include subclinical inborn errors or muscle metabolism, acquired muscle disorders, such as polymyositis, and strenuous exercise (e.g. long-distance running).²¹

Smita et al, reported a clinical case study, an asymptomatic patient, 66 years old female with persistent increase of aminotransferase. A physical examination revealed a healthy appearing female with no obvious abnormalities. All laboratory studies revealed normal results (including ALT, except an isolated increase in AST (544 U/L). They also concluded that persistent increase of AST was caused by a macroenzyme form. Macroenzymes are usually present due to the formation of an autoantibody enzyme complex, which has a higher molecular mass and a delayed clearance that leads to an increase in the amount of circulating enzyme. Identifying and documenting macroenzymes help preventing additional expensive testing and treatment.²⁵

CLINICAL APPROACH

Through close clinical approach, the majority patients (92%) with chronically elevated liver function tests were able to be diagnosed with the etiologies of the liver disease by history taking, physical examination, blood tests.¹² The history taking should be directed to identify risk factors for disease, with special attention on family history, medications, vitamin, herbal supplements, drug use, alcohol use, and blood product transfusions. The other significant health condition that can cause or augment liver transaminase elevation should be noted (type 2 diabetes, heart disease, thyroid disease, muscle disease, cancer) (Figure 1).^{6,26}

About 4-6 weeks after that, repeating liver biochemical tests may be helpful to exclude spurious results. When more than one of these tests provide abnormal findings, or the findings are persistently abnormal on serial determinations, the probability of liver disease is high. When all test results are normal, the probability of missing occult liver disease is low.²⁷

When the liver biochemical tests are still abnormal, other laboratories examination (ALT, AST, alkaline phosphates, bilirubin, albumin, prothrombin time, complete blood count, hepatitis A, B, C serologies and iron studies) should be done. Commonly, liver function tests are transiently abnormal after alcohol excess, minor viral illness, or drug reaction. An abnormal test result should be repeated after several weeks after lifestyle modification are conducted. Effective lifestyle modification includes complete abstinence from alcohol, control of diabetes and hyperlipidemia, weight loss in overweight, stopping hepatotoxic medications and supplements. In Sherwood et al, the abnormal test result resolved spontaneously in 38% of patients.⁵

Additional laboratory tests should be obtained when repeated liver biochemical were still elevated. Further serologic evaluation: ANA, anti-smooth muscle antibodies, ceruloplasmin, α -antitrypsin, antiendomysial and anti-tissue transglutaminase antibodies, and imaging (ultrasound, CT, MRI, as indicated) could be done. Ultrasound of the liver is especially performed if fatty infiltration is suspected (obese individuals, diabetics and or hyperlipidaemic patients).

The ability of clinicians deputed supported by laboratory and the liver imaging techniques to accurately diagnose patients with chronically abnormal liver test may be limited. In many instances imaging and biochemical testing cannot replace liver biopsy examination for definite determination of nature and extent of hepatic damage. Van Ness

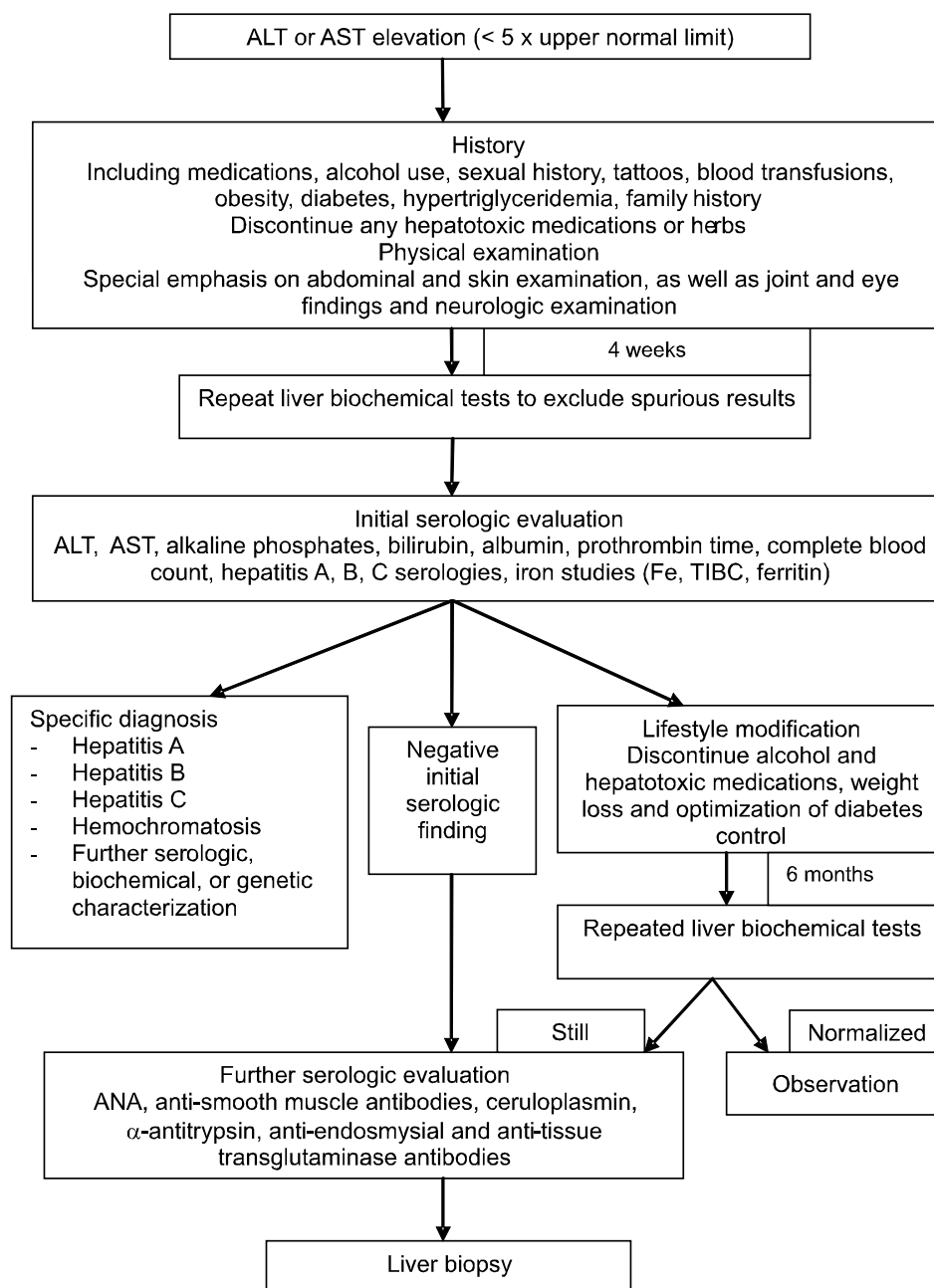


Figure 1. Evaluation of increased serum transaminase levels⁶

et al, conducted a study to determine diagnostic usefulness of percutaneous liver biopsy in evaluating patients with chronically liver-associated enzymes. The ability to diagnose clinically fatty liver, chronic necroinflammatory disease, and alcoholic liver disease was 56%, 81% and 88%, respectively.²⁸ In 8% of the patients with chronic abnormal ALT levels no cause is found.¹² So, if liver test abnormalities cannot be explained by other findings, liver biopsy examination can help to exclude serious liver disease or disclose the nature and severity of liver disease. Liver biopsy can provide important prognostic and diagnostic information regarding the cause of the liver disease but should be performed only if the expected benefit exceeds the small risk of the procedure.

CONCLUSION

Isolated alterations of biochemical markers of liver damage in seemingly healthy patient can present a challenge for the clinician. Mild elevation in liver chemistry tests such as ALT and AST can reveal serious underlying disease or have transient and benign etiologies. The majority patients with chronically elevated aminotransferase tests were able to be diagnosed with the etiologies of the liver disease by history taking, physical examination, and blood tests. The most common etiologies for chronic liver transaminase levels are alcohol use, non-alcoholic fatty liver disease, and viral hepatitis. In about 8% of patients with chronic abnormal ALT levels no cause was found. So, if liver test abnormalities cannot be

explained by other findings, liver biopsy examination can be considered to exclude serious liver disease or disclose the nature and severity of liver disease.

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