

Evaluation and Management of Abnormal Liver Chemistry Tests in the Asymptomatic Outpatient

Case Study and Commentary, *Laurel H. Hartwell, MD, and Jonathan M. Schwartz, MD*

Abstract

- **Objective:** To review the evaluation and management of liver enzyme abnormalities in asymptomatic patients.
- **Methods:** Review of the literature.
- **Results:** Liver chemistry tests include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, bilirubin, and gamma-glutamyltransferase (GGT). In general, AST and ALT abnormalities suggest a pattern of hepatocellular injury or necrosis, whereas alkaline phosphatase, bilirubin, and GGT elevations reflect cholestatic injury. A detailed history with attention paid to alcohol consumption, medication and herb or supplement use, travel history, and risk factors for viral hepatitis and metabolic syndrome can often quickly narrow the differential diagnosis. Nonalcoholic fatty liver disease is an increasing cause of chronic liver disease and should be approached in the context of the metabolic syndrome.
- **Conclusion:** A thorough understanding of the pathogenesis of abnormal liver chemistry tests, prevalence and risk factors of common liver diseases, and a clinically directed, stepwise approach to evaluation can help to avoid common pitfalls.

Serum liver chemistry tests are routinely acquired in clinical practice. Widespread testing in symptomatic or asymptomatic patients has identified many individuals with abnormal test results. Asymptomatic liver chemistry test abnormalities are estimated to occur in up to 4% of the U.S. population [1]. These abnormalities may affect eligibility for health care or life/disability insurance and employment or influence the use of potentially hepatotoxic medications. Furthermore, in addition to identifying liver disorders, abnormal liver chemistry tests related to nonalcoholic fatty liver disease (NAFLD) may have implications regarding risks of developing systemic disorders such as diabetes mellitus and cardiovascular disease.

Given the high prevalence of liver test abnormalities in the general population, understanding the etiologies of liver

enzyme abnormalities and implementation of thoughtful, cost-effective diagnostic and treatment strategies to evaluate patients with these disorders represents an important aspect of clinical practice.

CASE STUDY

Initial Presentation

 A 46-year-old man presents to his primary care physician to discuss abnormal liver chemistry results detected during a battery of laboratory tests taken when applying for life insurance.

History

The patient is asymptomatic and has a history of longstanding obesity, obstructive sleep apnea, “borderline” hypertension, and untreated hyperlipidemia. He drinks alcohol on rare occasions and may have received a blood transfusion following trauma to his left leg in a motor vehicle accident in 1983. He works as an administrator in a large corporation and is typically sedentary at work. He walks 2 miles twice a week.

Physical Examination

The patient is a well-appearing but overweight man with a blood pressure of 150/92 mm Hg, heart rate of 87 bpm, weight of 263 lb, and height of 73 inches (body mass index [BMI], 34.7 kg/m²). He is anicteric, without thyromegaly or jugular venous distention. Abdominal examination reveals an obese abdomen with mild hepatomegaly and a palpable spleen tip. He has no peripheral edema. Mild palmar erythema is present. No focal findings or asterixis were noted on the neurological examination.

Laboratory Evaluation

Laboratory testing reveals the following:

- Alanine aminotransferase (ALT) 64 U/L

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• Aspartate aminotransferase (AST)	43 U/L
• Alkaline phosphatase	125 U/L
• Total bilirubin	0.8 mg/dL
• Albumin	4.0 g/dL
• INR	0.8
• White blood cell count	5400/mm ³
• Platelets	142,000/mm ³
• Fasting glucose	123 mg/dL
• Creatinine	1.1 mg/dL

- What are the pathophysiologic mechanisms of liver chemistry test abnormalities?

Pathophysiology of Abnormal Liver Chemistry Tests

Liver chemistry tests include ALT, AST, alkaline phosphatase, bilirubin, and gamma-glutamyltransferase (GGT). In general, AST and ALT abnormalities suggest a pattern of hepatocellular injury or necrosis, whereas alkaline phosphatase, bilirubin, and GGT elevations reflect cholestatic injury. A "normal" test result is derived by calculating the mean of the laboratory value \pm 2 standard deviations of normal population. Hence the "normal" range varies according to the population tested; unless individuals with chronic liver disease are excluded from the studied population, the so-called normal value will likely misrepresent a truly normal population. For example, population mean and standard deviation for ALT and AST were much lower when patients with risk factors for liver disease were excluded [2]. Though normal ranges are usually set by individual laboratories based on their populations, some have called for a significant decrease in the accepted upper limits of normal for AST and ALT or correcting for sex and BMI [3]. Furthermore, tests commonly termed "liver chemistry tests" are not specific for the liver and may be abnormally elevated in conditions of injury to nonhepatic tissues such as skeletal muscle or the intestinal tract.

Aspartate Aminotransferase and Alanine Aminotransferase

These enzymes catalyze the transfer of amino groups to form pyruvate and oxaloacetate, respectively. They are released when hepatocytes are injured (either acutely or chronically), and can be readily assayed in the serum. While ALT is found predominantly in the cytosol of hepatocytes, AST is abundant both in the cytosol and mitochondria. AST is also

found in cardiac muscle, skeletal muscle, kidneys, brain, and blood, and for this reason high levels of ALT is considered to be more specific to the liver. Diurnal fluctuations can be seen in both AST and ALT, and significant increases may be seen following vigorous exercise. Muscle injury from a primary myositis or rhabdomyolysis can lead to significantly elevated ALT levels as well as AST levels. Of note, it has been shown that acute muscle injury secondary to extreme exercise can demonstrate an AST to ALT ratio of 5:1, as opposed to a chronic process such as polymyositis where the ratio is closer to equal, reflecting the shorter half-life of AST [4]. These are often elevated in acute biliary obstruction.

Bilirubin

Bilirubin is a heme degradation product that is insoluble in water. Conjugation via glucuronidation in hepatocyte allows the new water-soluble molecule to be subsequently excreted via canalicular transport systems through the biliary tree. Unconjugated (also known as indirect, based on early biochemical assays) hyperbilirubinemia may occur during hemolysis or in disordered glucuronyl transferase activity such as occurs in Gilbert's disease or more severe deficiencies of UDP-glucuronyltransferase (as in Crigler-Najjar syndrome). Conjugated (direct) hyperbilirubinemia occurs in mechanical biliary obstruction or conditions of impaired biliary excretion of bilirubin as a consequence of hepatocellular dysfunction. Conjugated hyperbilirubinemia occurs both in acute hepatitis and advanced chronic liver disease.

Alkaline Phosphatase

Alkaline phosphatases are metallophosphatases that are found in many tissues. The enzyme is predominantly present in the canalicular microvilli, as well as in bone and the small intestine. Alkaline phosphatase elevation occurs in conditions of extrahepatic biliary obstruction, infiltrative diseases of the liver, or due to certain medications. An elevated alkaline phosphatase level can be a normal finding in the third trimester of pregnancy as well as in an adolescent growth spurt.

Gamma-Glutamyltransferase

GGT, a microsomal enzyme, is present in hepatocytes, biliary epithelial cells, pancreas, kidneys, prostate, and intestine. Notably, it is not found in bone, and an elevated GGT can be used to confirm a hepatic source of alkaline phosphatase elevation. As a microsomal enzyme, it is inducible by many drugs, including alcohol, anticonvulsants, and warfarin.

Initial Assessment

 The patient has elevated aminotransferase levels with an AST/ALT ratio of 0.67, is asymptomatic, and without any signs of hepatic decompensation. He

demonstrates many of the cardinal features of the metabolic syndrome, which include obesity, diabetes, hypertension, and hypertriglyceridemia. On further questioning, he reports taking no regular medications and denies use of any herbs or supplements in the past year. His minimal use of alcohol is again confirmed. He has no history of injection drug or intranasal cocaine use, no tattoos, and no history of incarceration. He has no family history of liver disease or autoimmune diseases.

The physician strongly suspects NAFLD and decides on further workup to rule out other common causes of liver disease. A repeat set of liver chemistries, serologies for hepatitis A, B, and C, iron, total iron-binding capacity (TIBC), and ferritin are ordered. A liver ultrasound is ordered as well to evaluate for possible splenomegaly indicated on physical exam. Diet and weight loss are discussed in detail, and the patient is scheduled to meet with a diabetic nutritionist.

• **What is the best initial diagnostic approach to patients with asymptomatic liver chemistry abnormalities?**

A single elevated set of liver chemistry value in the asymptomatic outpatient can present a diagnostic dilemma to the physician. An immediate launch into an extensive investigation could prove costly, worrisome, and potentially harmful to the patient, but the early diagnosis of many liver diseases could prompt intervention to slow disease progression and decrease complications. The question of repeating the test versus proceeding with additional evaluation is often raised. Many chronic liver diseases such as hepatitis C infection demonstrate a waxing and waning pattern of mild aminotransferase elevation, and normal repeat values do not indicate resolution of disease. Normal liver chemistry values are not a guarantee of the absence of liver disease.

While some liver chemistry tests such as bilirubin can be used in conjunction with other laboratory values to formulate predictions about survival, as in the Model for End Stage Liver Disease (MELD) score [5], aminotransferases have traditionally been thought to function poorly as predictors of clinical outcomes. This is largely due to their inconsistent relationship to fibrosis and cirrhosis. A growing number of studies, though, have linked elevations in serum ALT to other outcomes, such as future development of metabolic syndrome, diabetes and cardiovascular disease [6,7].

A recent study of 1864 patients in the National Health and Nutrition Examination Survey III showed significant intraindividual variability in liver chemistry analysis when those tests were repeated (mean, 17 days apart). The investigators found that 38% of individuals with initially elevated bilirubin levels had normal levels on retesting, 36% of AST,

31% of ALT, 17% of alkaline phosphatase, and 17% of GGT. Results were not significantly different after excluding alcohol use, viral hepatitis, or BMI [8]. Though the authors recommended retesting all asymptomatic individuals with mild aminotransferase elevation before pursuing further evaluation, many still consider the clinical context and maintain a conservative approach of repeating liver chemistries at the time of initial workup.

A detailed history with attention paid to alcohol consumption, medication and herb or supplement use, travel history, and risk factors for viral hepatitis and metabolic syndrome can often quickly narrow the differential diagnosis. Physical examination should focus on identifying signs of portal hypertension such as splenomegaly and palmar erythema, decompensated liver disease, or potential extrahepatic etiologies, such as signs of congestive heart failure.

Mild AST and ALT Elevation (Figure 1)

Mild aminotransferase elevation (up to 5 times the upper limit of normal, as per the American Gastroenterological Association Clinical Practice Committee, 2002 [1]) is the most common alteration in liver chemistry found in outpatient practice, and typically is a result of chronic viral hepatitis or NAFLD (Table 1). Hepatitis C virus (HCV) has a prevalence of greater than 2% in the United States, and risk factors include intravenous or intranasal drug use, blood transfusions before July 1992, tattooing or piercing with unsterile needles, and possibly high-risk sexual activity (Table 2). Though many patients may not recall any known exposures, HCV antibody testing should always be part of the initial laboratory evaluation. Active HCV infection can be confirmed by HCV-RNA measurement.

Liver ultrasound is a common first step in those diagnosed with chronic HCV infection but cannot provide a reliable picture of the extent of fibrosis. The role of routine liver biopsy is controversial in these patients, but it should at least be considered, not only to direct decisions regarding therapy but also to guide hepatocellular carcinoma screening if cirrhosis is not otherwise readily apparent [9]. Various noninvasive markers have been developed to assess the extent of hepatic fibrosis. These include serum markers and techniques to measure liver elasticity. Though they have been shown to be most helpful in the setting of demonstrating minor to no fibrosis in those with HCV, they have yet to become part of routine clinical practice [10,11].

Chronic hepatitis B virus should be considered in patients who have similar risk factors as for HCV, and in those who have emigrated from regions of high prevalence such as Southeast Asia and sub-Saharan Africa. Vertical transmission is the most common risk factor in these regions, and as vertical transmission is associated with a higher rate of chronic infection than sexual transmission, the prevalence

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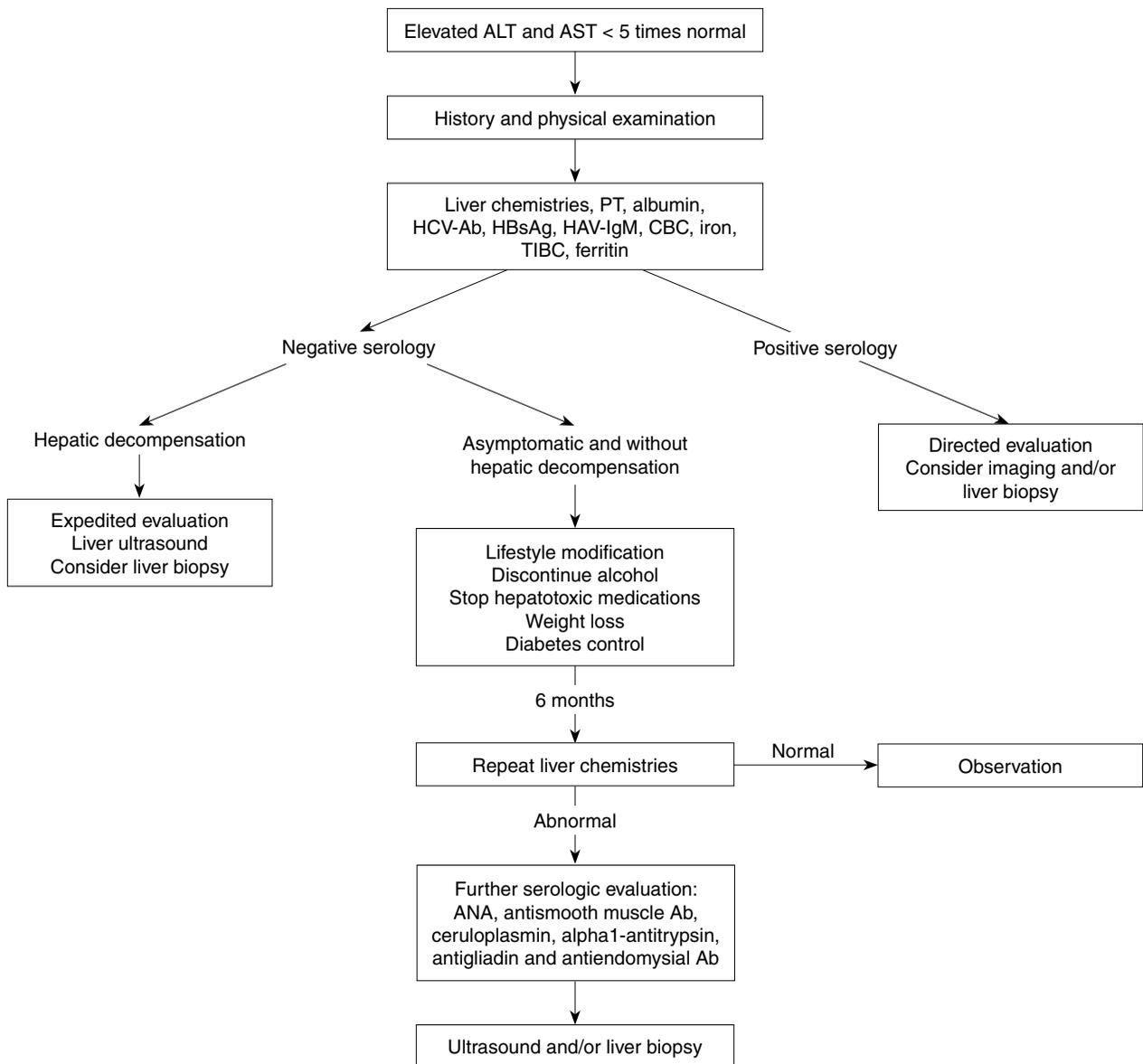


Figure 1. Algorithm for evaluation of mild elevations in transaminases. ALT = alanine aminotransferase; ANA = antinuclear antibody; AST = aspartate aminotransferase; CBC = complete blood count; PT = prothrombin time; TIBC = total iron-binding capacity. (Adapted with permission from American Gastroenterological Association medical position statement: evaluation of liver chemistry tests. *Gastroenterology* 2002;123:1365.)

of active disease is higher. If a patient is found to have active infection (positive hepatitis B surface antigen), further testing should be done of hepatitis B virus DNA viral load, e antigen antibody, and delta virus antibody. As in HCV, ultrasound and liver biopsy should be strongly considered. It is also appropriate to screen for HIV in patients with risk factors for hepatitis B or C. Though acute hepatitis A is rarely asymptomatic, we recommend testing for immunity along

with hepatitis A and B serologies in order to guide vaccination should chronic liver disease be found.

NAFLD is an increasingly common cause of liver injury in the United States, and is often suggested by the clinical picture as most patients are asymptomatic for much of the disease course. NAFLD and its more severe subset nonalcoholic steatohepatitis (NASH) are considered to be the hepatic manifestation of the metabolic syndrome, consisting of hy-

Table 1. Common Causes of Mild Aminotransferase Elevations

Chronic viral hepatitis
Alcohol
Steatosis/steatohepatitis
Medications
Hemochromatosis
Autoimmune hepatitis
Alpha-1 antitrypsin deficiency
Gluten sensitive enteropathy
Wilson's disease

perinsulinemia, obesity, diabetes, hypertension, and hypertriglyceridemia. The usual laboratory abnormalities include a mild aminotransferase elevation with ALT levels generally higher than AST levels. GGT and alkaline phosphatase may also be mildly elevated. Bilirubin and prothrombin time are usually normal, but a small number of patients may display a positive antinuclear antibody at low titers [12]. Iron stores may also be elevated. Ultrasound and computed tomography will identify fatty infiltration of the liver. In the appropriate clinical situation, a diagnosis of NAFLD can be made after other likely causes of liver diseases have been excluded.

Most drug-induced liver injury results in a pattern of aminotransferase elevation, but the degree of elevation does not always correspond to the degree of liver injury [13]. There is evidence that drug hepatotoxicity manifested by a hepatocellular pattern of injury along with jaundice is associated with significantly more mortality than hepatotoxicity with a cholestatic or mixed picture [14]. The medications most commonly associated with elevated aminotransferases include nonsteroidal anti-inflammatory drugs, antiepileptic drugs, statins, antibiotics, and antituberculosis drugs (Table 3). If a drug is suspected of causing liver injury, initial management should be to discontinue the medication and monitor liver chemistry tests as they normalize. Not infrequently a more detailed risk-benefit analysis must be made if the drug is essential and the aminotransferase elevation is mild. If, on the other hand, the aminotransferase elevation is rapidly progressive, the suspected medication should be immediately discontinued because of the risk of progression to liver failure.

As statins are used throughout the world with increasing frequency for treatment of hyperlipidemia and cardiovascular risk reduction, many clinicians are faced with the dilemma of a mild increase in transaminases that appear to be associated with statin initiation. Though a recent meta-analysis failed to show a significant increase in liver enzyme elevations in those taking statins compared to pla-

Table 2. Risk Factors for Hepatitis C Infection

Intravenous or intranasal drug use
Blood product transfusion or organ transplant before 1992
Clotting factor transfusion before 1987
Tattooing or piercing with unsterile equipment
High-risk sexual behavior

cebo, it remains a clinical concern [15]. Though no specific pattern of liver injury (cholestatic, hepatocellular, or mixed) appears to predominate, liver enzymes generally decrease after cessation or dose reduction [16]. The incidence of clinically significant liver injury associated with statins appears to be quite low, and in most patients without cirrhosis and decompensated liver disease the benefits likely outweigh the risks of use.

Hereditary hemochromatosis is a relatively common autosomal recessive disorder, and a detailed family history is often helpful. Further testing should include serum iron and serum ferritin. A calculated transferrin saturation index greater than 45% is highly suggestive of hereditary hemochromatosis [17], but iron overload is frequently found in other liver diseases. A number of different mutations have been identified and are best described in those of Northern European descent. Other mutations may occur in ethnicities other than Northern European but are less well described.

An AST-predominant transaminase elevation is frequently a result of alcohol use. A detailed alcohol history can be difficult to obtain, and corroborating information from family members can be helpful. The pattern most often seen is an AST:ALT ratio of approximately 2:1, and absolute AST values rarely exceed 300 U/L [18,19]. The diagnosis depends on the clinical history of alcohol use, as NAFLD in turn depends on the clinical history of minimal to no alcohol use. Liver biopsy can demonstrate the range of hepatitis to steatosis, fibrosis and cirrhosis, and may be similar in appearance to NASH. A trial of alcohol cessation with subsequent normalization of transaminases can prove diagnostic, though the patient should also receive screening for viral infection and iron overload, as above.

If initial history, physical examination, and evaluation with hepatitis A, B, and C serologies and iron studies are unrevealing, other less common causes of transaminase elevation should be considered. Autoimmune hepatitis is more common in female patients and is often associated with thyroid disease, inflammatory arthritis, and other autoimmune conditions. Serologic evaluation includes antinuclear antibodies, anti-smooth muscle antibodies, liver-kidney microsomal antibodies, and serum globulin levels. Diagnosis is not always clear-cut, and liver biopsy is often required [20]. Wilson's disease is a consideration for patients under age

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Table 3. Patterns of Drug-Induced Liver Injury

Hepatocellular (Elevated ALT)		Mixed (Elevated AP + ALT)	Cholestatic (Elevated AP + TBL)
Acarbose	Losartan	Aimtriptyline	Amoxicillin-clavulanic acid
Acetaminophen	Methotrexate	Azathioprine	Anabolic steroids
Allopurinol	NSAIDs	Capropril	Chlorpromazine
Amiodarone	Omeprazole	Carbamazepine	Clopidogrel
Baclofen	Paroxetine	Clindamycin	Oral contraceptives
Bupropion	Pyrazinamide	Cyproheptadine	Erythromycins
Fluoxetine	Rifampin	Enalapril	Estrogens
HAART drugs	Risperidone	Flutamide	Irbesartan
Herbals*	Sertraline	Nitrofurantoin	Mirtazapine
Chaparral	Statins	Phenobarbital	Phenothiazines
Germander	Tetracyclines	Phenytoin	Terbinafine
Kava kava	Trazadone	Sulfamides	Tricyclics
Isoniazid	Trovafloxacin	Trazadone	
Ketokonazole	Valproic acid	TMP-SMX	
Lisinopril		Verapamil	

ALT = alanine aminotransferase; AP = alkaline phosphatase; HAART = highly active antiretroviral therapy; NSAIDs = nonsteroidal anti-inflammatory drugs; TBL = total bilirubin; TMP-SMX = trimethoprim-sulfamethoxazole. (Adapted from Navarro VJ, Senior JR. Drug-related hepatotoxicity. *N Engl J Med* 2006;354:731–9.)

*Listed are the most commonly used hepatotoxic herbal preparations, though many others have been identified.

40 years, and diagnostic evaluation includes serum ceruloplasmin levels a slit-lamp examination for Kayser-Fleischer rings, urinary copper levels, and liver biopsy for copper deposition. Alpha-1 antitrypsin deficiency is not commonly diagnosed in adults, but assays show decreased levels of alpha-1 antitrypsin and the lack of a peak in alpha-globulin bands on serum protein electrophoresis. Definitive diagnosis is made by phenotype analysis and confirmed on liver biopsy. Finally, celiac disease has been associated with transaminitis, and can be screened for with serum tissue transglutaminase levels or anti-gliadin and anti-endomysial antibodies. Liver chemistry abnormalities will often resolve with initiation of a gluten-free diet [21].

It is important to note that as liver disease progresses to cirrhosis, an AST-predominant pattern may emerge regardless of the underlying etiology [22]. AST-predominant aminotransferase elevation may also be a clue to a nonhepatic etiology. Disorders to consider include myopathy, hemolysis, thyroid disease, strenuous exercise, and macro-AST. Inflammatory myopathies are generally associated with high levels of serum creatine kinase (CK), AST, and lactate dehydrogenase. In the absence of CK, these patients are often first evaluated extensively for liver disease before a myopathic process is identified. As weakness can develop slowly over weeks to months, patients may be relatively asymptomatic at the time of initial laboratory analysis. If workup is persistently unrevealing or the physician suspects nonhepatic

etiology, further constitutional symptoms should be elicited, such as malaise, weight loss, and arthralgias. Though often overlapping with symptoms of liver disease, CK evaluation can be helpful, and electromyography and muscle biopsy can be considered and next steps [23].

Severe AST and ALT Elevations

Elevations of AST and ALT greater than 10 to 15 times the upper limit of normal are less often incidental findings in the asymptomatic outpatient, and a careful history and physical often reveal signs and symptoms of underlying etiology or hepatic decompensation. Though outside the scope of this review, the differential is narrow and warrants a brief discussion. The very highest aminotransferase elevations (≥ 15 times the upper limit of normal) are most often a result of toxic or ischemic hepatic injury rather than viral hepatitis [24]. Acetaminophen overdose is a common cause of acute liver failure, especially in the United Kingdom and the United States, but overdose of herbal remedies is becoming increasingly common. Ischemic injury usually occurs in the setting of sepsis, arrhythmias, hypotension, hemorrhage or other low-flow states, and the clinical scenario, rather than laboratory pattern, often indicates the etiology. Acute viral hepatitis is important to recognize as some patients may benefit from immediate antiviral treatment. Autoimmune hepatitis, Wilson's disease, Budd-Chiari Syndrome, and acute biliary obstruction should also be considered.

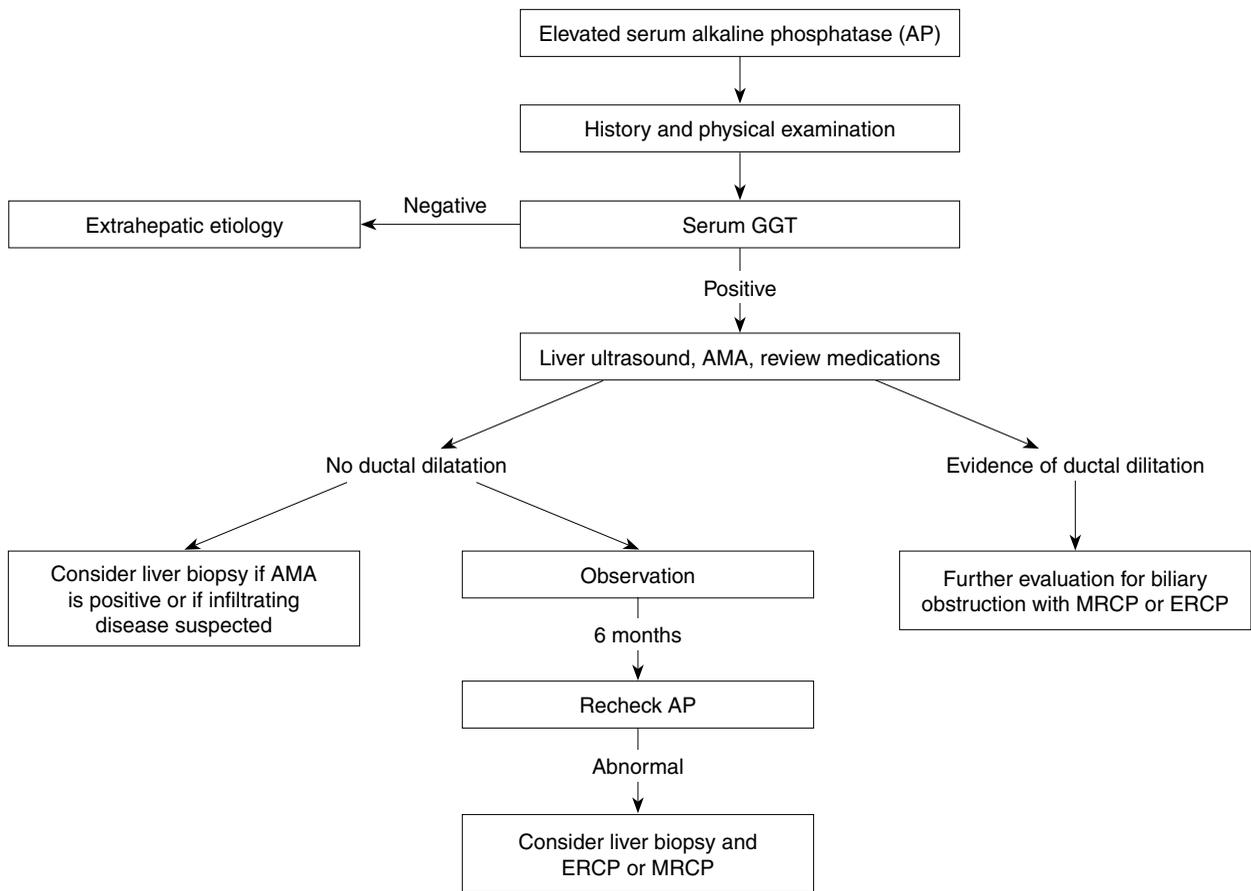


Figure 2. Algorithm for evaluation of elevated serum alkaline phosphatase. AMA = antimitochondrial antibodies; ERCP = endoscopic retrograde cholangiopancreatography; GGT = gamma-glutamyltransferase; MRCP = magnetic resonance cholangiopancreatography. (Adapted from American Gastroenterological Association medical position statement: evaluation of liver chemistry tests. *Gastroenterology* 2002;123:1365.)

Elevated Alkaline Phosphatase (Figure 2)

Alkaline phosphatase elevations, either alone or in conjunction with elevated bilirubin, are part of a pattern of cholestatic or infiltrative disease. If other liver chemistries such as AST, ALT, and bilirubin are also elevated, an elevated alkaline phosphatase is generally considered to be hepatic in origin. If, on the other hand, it is encountered in isolation, the source must be identified. Isoenzyme determination by gel electrophoresis is possible, but not commonly done in clinical practice, and most clinicians use serum levels of GGT. Serum GGT levels are elevated in liver dysfunction but not in patients with bone disease. As both cholestatic disease (primary biliary cirrhosis, partial bile duct obstruction, primary sclerosing cholangitis) and infiltrative disease (malignancy and granulomatous disease) can cause anatomic changes in either the bile ducts or the liver parenchyma, an

ultrasound of the liver is a helpful first step. Other unusual or atypical cholangiopathies that can cause increased alkaline phosphatase include antimitochondrial antibody negative primary biliary cirrhosis, small duct primary sclerosing cholangitis and autoimmune cholangitis [25].

Drug-induced cholestasis can be caused by many common medications such as estrogens and angiotensin-converting enzyme inhibitors, and ultrasound is often relatively normal. A serum antimitochondrial antibody, highly associated with primary biliary cirrhosis, should be checked initially, at the same time as the ultrasound. If there is evidence of bile duct dilatation on ultrasound, magnetic resonance cholangiopancreatography (MRCP), or endoscopic retrograde cholangiopancreatography (ERCP) should be pursued, based on the clinical situation. If the patient has known or suspected inflammatory bowel disease, antineutrophil

cytoplasmic antibodies should also be ordered in the assessment of primary sclerosing cholangitis. If serology is negative and serum alkaline phosphatase levels remain elevated for more than 6 months, liver biopsy should be considered.

Elevated Gamma-Glutamyltransferase

GGT elevation often occurs in a similar cholestatic pattern as alkaline phosphatase, and as described above can be useful in delineating hepatic versus bone origin of alkaline phosphatase. Though very sensitive for liver disease, GGT is not specific, and elevations can also be seen in chronic obstructive pulmonary disease, postmyocardial infarction, and renal disease. In addition to bile duct disease and autoimmune cholestatic disease, other primary hepatic disorders such as fatty liver disease and hepatitis C infection can lead to elevations in GGT [26]. Some studies have linked GGT elevations specifically to alcohol use [27], but it has greater utility in the setting of other patterns of alcoholic liver injury, such as an AST to ALT ratio of at least 2:1. Studies have shown GGT to be associated with development of the metabolic syndrome [28] as well as mortality from all causes, liver disease, cancer, and diabetes [29].

Unconjugated Hyperbilirubinemia

Elevated serum bilirubin in the asymptomatic outpatient should initially be fractionated into conjugated and unconjugated levels, especially if aminotransferase levels are not also concurrently elevated. An isolated unconjugated hyperbilirubinemia is a common finding in the general population, and anywhere from 5% to 10% of Caucasians are estimated to have Gilbert's syndrome [30,31]. When evaluating an elevation in serum unconjugated bilirubin, the 2 principal underlying mechanisms must be considered: increased production of bilirubin or decreased hepatic conjugation. Hemolysis is perhaps the most common cause of unconjugated bilirubin overproduction and can be evaluated with a complete blood count, reticulocyte count, lactate dehydrogenase, and haptoglobin. Less frequently, reabsorption of a large hematoma (with associated elevated CK and lactate dehydrogenase levels) or ineffective erythropoiesis can cause an unconjugated hyperbilirubinemia. Once hemolysis or medication use has been ruled out, Gilbert's syndrome should be considered. In this disorder, polymorphisms in the UDP-glucuronyltransferase gene lead to a decreased ability to conjugate bilirubin, and patients exhibit a mild unconjugated hyperbilirubinemia (< 4 mg/dL) in the absence of aminotransferase or alkaline phosphatase elevations. Liver ultrasound is normal. A number of further provocative tests may be ordered to confirm the genetic defect, but the diagnosis is most often a clinical one. Other disorders of bilirubin conjugation include Crigler-Najjar disease and shunt hyperbilirubinemia.

Conjugated Hyperbilirubinemia

Though often considered to be predominantly a marker of cholestatic disease, a conjugated hyperbilirubinemia can be found in hepatocellular liver disease and drug/toxin injury as well as in intra- and extrahepatic cholestasis. As above, the most important initial step in evaluating hyperbilirubinemia is determining the conjugated versus unconjugated fraction. If there is concomitant alkaline phosphatase elevation, a right upper quadrant ultrasound should be obtained to evaluate for signs of biliary obstruction. If evidence of ductal dilatation is present, further studies such as MRCP or ERCP may be warranted. If there is no evidence of bile duct obstruction on imaging, further evaluation should be driven by the clinical scenario and include a similar approach as for elevated AST/ALT. If an antimitochondrial antibody is negative and all suspected medications/toxins are reviewed or discontinued, imaging with MRCP and possibly a liver biopsy may be warranted. Again, the clinical scenario may point to less common causes: Dubin-Johnson and Rotor syndrome are relatively rare genetic disorders of bile secretion, vanishing bile duct syndrome can be seen post liver transplant or in drug reactions, intrahepatic cholestasis can develop in pregnancy, and a conjugated hyperbilirubinemia can be seen in patients on total parental nutrition.

Further Patient Management

 The patient is seen again in clinic to review test results. Serologic evaluation shows immunity to hepatitis A but no evidence of exposure to hepatitis B or C. Iron is 75 ng/dL, ferritin is 150 ng/mL, and transferrin saturation is 20%. AST and ALT remain elevated. Abdominal ultrasound demonstrates an enlarged and hyperechoic liver without discrete masses and an enlarged spleen. The patient is referred to a gastroenterologist, who decides to perform a liver biopsy. Histology shows centrilobular macrovesicular steatosis, ballooning hepatocytes, Mallory's hyaline, and stage 3 fibrosis. The patient is diagnosed with NASH and given extensive counseling on weight loss and control of diabetes. He is vaccinated against hepatitis B, and the gastroenterologist plans on seeing him back again in 6 months.

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- **What is the etiology of nonalcoholic fatty liver disease, and what treatments are available?**
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NAFLD, defined as macrovesicular hepatic steatosis in the absence of significant alcohol consumption, encompasses a range of both etiology and severity. NASH is a more severe form of this process, and demonstrates a histologic pattern of moderate to severe steatosis, hepatocyte ballooning, lobu-

lar inflammation, fibrosis, and Mallory's hyaline [32]. While NAFLD and NASH can be caused by a range of conditions including lipid disorders, severe weight loss, total parental nutrition, toxins, and drugs, it is the strong association with insulin resistance that has been of particular recent interest. NAFLD is now widely recognized as the hepatic manifestation of the metabolic syndrome, a combination of abdominal obesity, elevated triglycerides, low high-density lipoprotein cholesterol, hypertension, and elevated fasting glucose.

The prevalence of NAFLD has been difficult to determine. While a number of studies have indicated that up to 20% of the general population in industrialized countries may have NAFLD and 2% to 3% NASH [33], others estimate a prevalence of NAFLD as high as 30% in the urban United States [34]. Recent studies have shown that insulin resistance may be the most important driving force in the development of NASH, and that the features of insulin resistance are specific to NASH rather than obesity or chronic liver disease alone [35]. Though NASH is often asymptomatic in its early stages, patients can present with right upper quadrant abdominal discomfort, hepatomegaly, and any of the general stigmata of chronic liver disease. Laboratory analysis shows an AST-predominate transaminitis, usually less than 300 U/L. Though NAFLD can be diagnosed clinically by the findings of hyperechogenicity of the liver on ultrasound in the setting of a convincing lack of alcohol use, the diagnosis of NASH requires liver biopsy for direct histological assessment. While it is generally believed that nonalcoholic fatty liver alone carries little risk of progressing over time to fibrosis and cirrhosis, patients diagnosed with NASH have a more uncertain future and are at higher risk for developing cirrhosis [36].

Management of NASH includes treatment of the underlying metabolic syndrome risk factors, prevention of further liver injury, and therapies targeted at the process of NASH itself [37]. Gradual weight loss through diet and exercise are the foundation of this approach, with consideration for surgical weight loss options in those with a BMI greater than 40 kg/m². It is recommended to limit alcohol use, avoid hepatotoxic medications, and vaccinate against hepatitis A and B if not immune. Investigations into specific pharmacologic therapy of NASH itself are currently focused on insulin sensitization. Several studies have looked at thiazolidinediones, and a recent trial of pioglitazone in 74 nondiabetic patients with NASH showed significant improvement in the histologic markers of NASH [38]. Metformin has been shown to improve ALT and insulin sensitization but not liver histology [39,40]. The use of these medications is currently based on a few small trials, and further studies are required before they become part of routine clinical practice. Other agents under investigation include ursodeoxycholic acid, probucol, betaine, vitamin E, pentoxifyline, and gemfibrozil.

Further Patient Management

 After 3 months the patient returns to the gastroenterologist for follow-up. He has lost only 2 lb and his blood sugars have not been adequately controlled on his new diabetic diet. Repeat liver chemistries show an ALT of 92 U/L, AST of 57 U/L, alkaline phosphatase of 130 U/L, total bilirubin of 0.7 mg/dL, albumin of 4 g/dL, INR 0.8. Pioglitazone is initiated as well as a statin. The patient works closely with his primary care physician on weight loss and control of his diabetes, and at 6 months has lost 10 lb. Liver chemistries are checked every 6 months. Though he does not yet have cirrhosis, his physician begins surveillance for hepatocellular carcinoma since sampling variation may understage the extent of hepatic fibrosis. In addition, it is often difficult to determine precisely when patients progress from stage 3 fibrosis to cirrhosis, and repeat liver biopsy is not indicated solely for this reason [41].

CONCLUSION

Liver chemistry tests are frequently checked in clinical practice for a variety of reasons, and abnormalities are often detected. Mild abnormal results in an asymptomatic patient can be a challenge to the primary care provider who wishes to exclude the early stages of serious liver disease but avoid unnecessary, expensive, and potentially harmful tests. A thorough understanding of the pathogenesis of abnormal liver chemistry tests, prevalence and risk factors of common liver diseases, and a clinically directed, stepwise approach to evaluation can help to avoid common pitfalls.

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