Primary Care

Evaluation of Abnormal Liver-Enzyme Results in Asymptomatic Patients

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NOW that routine laboratory testing is automated and is frequently part of an annual checkup, physicians are often faced with the problem of a patient with one abnormal result on measurement of serum aminotransferases or alkaline phosphatase but no symptoms. Many batteries of screening tests now include measurement of serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and γ-glutamyltransferase. Although these enzymes are present in tissues throughout the body, they are most often elevated in patients with liver disease and may reflect liver injury.

The first step in the evaluation of a patient with elevated liver-enzyme levels but no symptoms is to repeat the test to confirm the result. If the result is still abnormal, the physician should evaluate the degree of the elevation. A minor elevation (less than twice the normal value) may be of no clinical importance if the disorders listed in Table 1 have been ruled out and, in fact, may not even be abnormal. The normal range for any laboratory test is the mean value in a group of healthy persons ±2 SD. Thus, 5 percent of the results obtained from these normal persons fall outside the defined normal range, 2.5 percent of which may be above the upper limit of normal. There are also circumstances in which elevations in liver-enzyme levels are physiologic; for example, alkaline phosphatase levels are increased in healthy women during the third trimester of pregnancy. The evaluation of the patient with an isolated elevation of an aminotransferase differs from that for a patient with an isolated elevation of alkaline phosphatase or γ-glutamyltransferase.

AMINOTRANSFERASE LEVELS

Aminotransferase levels are sensitive indicators of liver-cell injury and are helpful in recognizing hepatocellular diseases such as hepatitis.[1] Both aminotransferases are normally present in serum at low levels, usually less than 30 to 40 U per liter. The normal range varies widely among laboratories. Some researchers recommend adjusting aminotransferase values for sex and body-mass index,[2] but these adjustments are rarely made. Aspartate aminotransferase is found, in decreasing order of concentration, in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes. The highest level of alanine aminotransferase is in the liver, and levels of this enzyme are accordingly more specific indicators of liver injury. Both enzymes are released into the blood in increasing amounts when the liver cell membrane is damaged. Necrosis of liver cells is not required for the release of the aminotransferases. In fact, there is poor correlation between the degree of liver-cell damage and the level of the aminotransferases.[1] If the aminotransferase levels are normal on retesting, no further evaluation is necessary. If the results of repeated tests remain abnormal, further evaluation is indicated.

The first step in the evaluation is to obtain a complete history in an effort to identify the most common causes of elevated aminotransferase levels: alcohol-related liver injury, chronic hepatitis B and C, autoimmune hepatitis, hepatic steatosis (fatty infiltration of the liver), nonalcoholic steatohepatitis, hemochromatosis, Wilson's disease, alpha$_1$-antitrypsin deficiency, and a recently recognized cause, celiac sprue (Table 1). Table 2 lists the blood tests that can be used to identify many of these disorders. It is more efficient to order all the blood tests in the first group initially, unless the history strongly suggests a definite diagnosis, such as alcohol abuse. The cause of the aminotransferase elevation can usually be identified on assessment of the pattern of the results of liver-enzyme tests and additional testing.

The cause of an elevated alanine aminotransferase level varies greatly depending on the population studied. Among 19,877 Air Force trainees who volunteered to donate blood, 99 (0.5 percent) had elevated alanine aminotransferase levels.[3] A cause for the elevation was found in only 12: 4 had hepatitis B, 4 had hepatitis C, 2 had autoimmune hepatitis, 1 had cholelithiasis, and 1 had acute appendicitis. In a group of 100 consecutive blood donors with elevated alanine aminotransferase levels, 48 percent had changes related to alcohol use, 22 percent had fatty liver, 17 percent had hepatitis C, 4 percent had another identified problem, and in the remaining 9 percent, no specific diagnosis was made.[4] In another study of 149 asymptomatic patients with elevated alanine aminotransferase levels who underwent liver biopsy, 56 percent had fatty liver, 20 percent had non-A, non-B hepatitis, 11 percent had changes related to alcohol use, 3 percent had hepatitis B, 8 percent had other causes, and in 2 percent, no cause was identified.[5] A recent study assessed 1124 consecutive patients who were referred for chronic elevations in aminotransferase levels.[6] Eighty-one of these patients had no definable cause of the elevation and underwent a

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TABLE 1. CAUSES OF CHRONICALLY ELEVATED
AMINOTRANSFERASE LEVELS.

Hepatic causes
Alcohol abuse
Medication
Chronic hepatitis B and C
Steatosis and nonalcoholic steatohepatitis
Autoimmune hepatitis
Hemochromatosis
Wilson's disease (in patients ≤40 years old)
Alpha$_1$-antitrypsin deficiency

Nonhepatic causes
Celiac sprue
Inherited disorders of muscle metabolism
Acquired muscle diseases
Strenuous exercise

TABLE 2. LABORATORY TESTS THAT MAY IDENTIFY THE CAUSE
OF ELEVATED AMINOTRANSFERASE LEVELS IN A PATIENT
WITH NO SYMPTOMS.

TEST	DIAGNOSIS
Initial tests	
Test for hepatitis C antibody in serum	Presence of hepatitis C antibody indicates chronic hepatitis C
Test for hepatitis B surface antigen, surface antibody, and core antibody in serum	Presence of hepatitis B surface antigen and core antibody indicates chronic hepatitis B
Measurement of serum iron and total iron-binding capacity	Iron overload suggests hemochromatosis
Measurement of serum ceruloplasmin	Decreased ceruloplasmin levels suggest Wilson's disease (if patient is ≤40 years old)
Serum protein electrophoresis	Increase in polyclonal immunoglobulins suggests autoimmune hepatitis
Serum protein electrophoresis	Marked decrease in α-globulin bands suggests alpha$_1$-antitrypsin deficiency
Additional tests*	
Reverse-transcriptase polymerase chain reaction for hepatitis C virus RNA	Presence of viral RNA indicates chronic hepatitis C
Alpha$_1$-antitrypsin phenotyping	Presence of the ZZ phenotype indicates alpha$_1$-antitrypsin deficiency
Tests for antiendomysial and antigliadin antibodies in serum	Presence of antibodies indicates celiac sprue
Measurement of creatine kinase and aldolase	Elevated enzyme levels indicate disorders of striated muscle

*If the results of the initial set of tests are normal, these additional tests
may pinpoint the cause.

liver biopsy. Of these 81 patients, 41 had steatosis,
26 had steatohepatitis, 4 had fibrosis, 2 had cirrhosis, and 8 had normal histologic findings. The patients with histologic evidence of fibrosis and cirrhosis also had evidence of fatty metamorphosis. None
of the biopsies yielded a specific diagnosis except those
showing steatosis and steatohepatitis.

CAUSES OF ELEVATED AMINOTRANSFERASE LEVELS

Alcohol Abuse

The diagnosis of alcohol abuse can be difficult because many patients conceal information about their
alcohol use. The diagnosis is supported by the finding of a ratio of aspartate aminotransferase to alanine
aminotransferase of at least 2:1. In a study of hundreds of patients who had histologically confirmed
liver disorders, more than 90 percent of the patients
who had an aspartate aminotransferase:alanine aminotransferase ratio of at least 2:1 had alcoholic liver
disease.[7] The percentage increased to more than 96
percent when the ratio was greater than 3:1. The increased ratio reflects primarily the low serum activity
of alanine aminotransferase in patients with alcoholic liver disease. This decrease is due to an alcohol-related deficiency of pyridoxal 5-phosphate.[8]

Measurement of γ-glutamyltransferase may also be
helpful in diagnosing alcohol abuse. A γ-glutamyltransferase level that is twice the normal level in patients with an aspartate aminotransferase:alanine aminotransferase ratio of at least 2:1 strongly suggests
the diagnosis of alcohol abuse. However, the lack of
specificity of the γ-glutamyltransferase level precludes
its use as a single test to diagnose alcohol abuse.

The degree of elevation of aminotransferase levels
may also be helpful in identifying alcohol abuse. It
is rare for the aspartate aminotransferase level to be
more than eight times the normal value in patients
with alcohol abuse, and it is even less common for
the alanine aminotransferase level to be more than
five times the normal value in such patients.[7] In fact,
the alanine aminotransferase level may be normal, even
in patients with severe alcoholic liver disease.

Medication

A careful history-taking and meticulous review of
laboratory data are critical for identifying a medication as the cause of elevated aminotransferase levels.
A drug effect is a possibility if the increase in liver-enzyme levels was associated with the initiation of a
medication. Almost any medication can cause an elevation in liver-enzyme levels. Common ones include
nonsteroidal antiinflammatory drugs, antibiotics, antiepileptic drugs, inhibitors of hydroxymethylglutaryl−coenzyme A reductase, and antituberculosis drugs
(Table 3). In addition to medications, herbal preparations and illicit drugs or substances may cause elevations in liver-enzyme levels (Table 3).

The easiest way to determine whether a medication is responsible for the elevation is to stop treatment and see whether the test results return to normal. If the identified medication is essential to the
patient's well-being and no suitable substitute is available, the physician needs to make a risk−benefit analysis to determine whether the drug should be contin-

TABLE 3. MEDICATIONS, HERBS, AND DRUGS OR SUBSTANCES OF ABUSE REPORTED TO CAUSE ELEVATIONS IN LIVER-ENZYME LEVELS.

Medications

Antibiotics
    Synthetic penicillins
    Ciprofloxacin
    Nitrofurantoin
    Ketoconazole and fluconazole
    Isoniazid
Antiepileptic drugs
    Phenytoin
    Carbamazepine
Inhibitors of hydroxymethylglutaryl–coenzyme A reductase
    Simvastatin
    Pravastatin
    Lovastatin
    Atorvastatin
Nonsteroidal antiinflammatory drugs
Sulfonylureas for hyperglycemia
    Glipizide

Herbs and homeopathic treatments

Chaparral
Chinese herbs
    Ji bu huan
    Ephedra (mahuang)
Gentian
Germander
Alchemilla (lady's mantle)
Senna
Shark cartilage
Scutellaria (skullcap)

Drugs and substances of abuse

Anabolic steroids
Cocaine
5-Methoxy-3,4-methylenedioxymethamphetamine
    (MDMA, "ecstasy")
Phencyclidine ("angel dust")
Glues and solvents
    Glues containing toluene
    Trichloroethylene, chloroform

ued despite the elevation in aminotransferase levels. Often, consultation with a hepatologist is necessary. Occasionally, a liver biopsy is necessary to determine the nature and severity of liver injury.

Chronic Hepatitis

Chronic hepatitis C is very common in the United States. Approximately 3.9 million Americans are positive for antibodies against hepatitis C, and an estimated 2.7 million people are considered to be chronically infected on the basis of the presence of hepatitis C virus RNA in serum.[9] The risk of chronic infection is highest in patients with a history of parenteral exposure to the virus (e.g., because of blood transfusions, intravenous drug use, or work-related duties), cocaine use, tattoos, body piercing, and high-risk sexual behavior.

The initial test for hepatitis C infection is serologic testing for the hepatitis C antibody. The testing has a sensitivity of 92 to 97 percent, depending on the assay.[10] A positive test in a patient with risk fac-

tors for infection is sufficient to make the diagnosis, but the diagnosis is usually confirmed by measurement of serum levels of hepatitis C virus RNA with use of the reverse-transcriptase polymerase chain reaction. This approach is currently the gold standard for detecting hepatitis C infection.[10] A positive test should prompt consideration of a liver biopsy to assess the severity of damage. Patients with chronic hepatitis C and evidence of fibrosis are usually treated.

Initial tests for hepatitis B infection include serologic tests for hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody. A positive test for hepatitis B surface antibody and core antibody indicates the presence of immunity to hepatitis B, and another cause for the elevated aminotransferase levels should be sought. A positive test for hepatitis B surface antigen and core antibody indicates the presence of infection. Tests to determine whether there is viral replication, including serologic tests for hepatitis B e antigen, hepatitis B e antibody, and hepatitis B virus DNA, should be undertaken. In patients with positive tests for hepatitis B virus DNA and hepatitis B e antigen, liver biopsy and treatment should be considered.

Autoimmune Hepatitis

Autoimmune hepatitis occurs primarily in young-to-middle-aged women.[11] The ratio of female patients to male patients is 4:1.[12] The diagnosis is based on the presence of elevated aminotransferase levels, the absence of other causes of chronic hepatitis, and serologic and pathological features suggestive of the disease.[12] A useful screening test is serum protein electrophoresis. More than 80 percent of patients with autoimmune hepatitis have hypergammaglobulinemia.[13] However, a finding of more than twice the normal level of polyclonal immunoglobulins is most suggestive of the diagnosis. Additional tests that are commonly ordered include serologic tests for antinuclear antibodies, antibodies against smooth muscle, and liver–kidney microsomal antibodies. The first two tests have reported sensitivities of 28 percent and 40 percent, respectively.[13] The third test is rarely positive among patients in the United States, Australia, and Japan.[12] We do not recommend the routine use of these three tests for the diagnosis of autoimmune hepatitis. A liver biopsy is essential to confirm the diagnosis.

Hepatic Steatosis and Nonalcoholic Steatohepatitis

The only clinical evidence of hepatic steatosis and a condition that may be associated with it, nonalcoholic steatohepatitis, may be mild elevations in aminotransferase levels. The levels are usually less than four times the normal value.[14,15] In contrast to patients with alcohol-related liver disease, patients with nonalcoholic steatohepatitis usually have an aspartate aminotransferase:alanine aminotransferase ratio that

is less than 1:1.[15,16] Fatty infiltration of the liver can be identified by ultrasonography or computed tomography. Ultrasonography should be part of the evaluation of patients with chronically elevated aminotransferase levels. The diagnosis of nonalcoholic steatohepatitis requires a liver biopsy. In addition to fatty infiltration, the histologic findings in patients with nonalcoholic steatohepatitis include pericentral fibrosis, inflammation, liver-cell necrosis, and hyaline cytoplasmic inclusions in hepatocytes that are identical to Mallory's bodies, which are characteristic of alcoholic liver disease.[14]

The two conditions have different natural histories: steatosis appears to have a benign course, whereas nonalcoholic steatohepatitis can progress to cirrhosis.[17] Liver failure as a result of nonalcoholic steatohepatitis is uncommon. Weight loss is the cornerstone of treatment in patients who are obese.[18] Other treatments for nonalcoholic steatohepatitis that are being studied include vitamin E and ursodiol. Vitamin E was associated with decreases in alanine aminotransferase and aspartate aminotransferase levels and in histologic abnormalities in two pilot studies.[19,20] Ursodiol decreased alanine aminotransferase and aspartate aminotransferase levels but not the histologic abnormalities in another pilot study.[21]

Hemochromatosis

Hereditary hemochromatosis is a common genetic disorder.[22] Cost-effective screening starts with the measurement of serum iron and total iron-binding capacity (Table 2). A transferrin-saturation value (obtained by dividing the serum iron level by the total iron-binding capacity) of more than 45 percent is suggestive of hemochromatosis.[22] Measurement of serum ferritin provides less specific information, because it is an acute-phase reactant.

If screening tests suggest the presence of iron overload, a liver biopsy should be performed to assess hepatic iron levels and the severity of liver damage. A hepatic iron index (the hepatic iron level in micromoles per gram of dry weight divided by the patient's age) of more than 1.9 is consistent with the presence of homozygous hereditary hemochromatosis.[22] Genetic testing is now available to identify the mutation in the hemochromatosis (*HFE*) gene that causes the majority of cases. A liver biopsy is not necessary for patients with hereditary hemochromatosis who are younger than 40 years of age and who have normal liver function.

Wilson's Disease

Wilson's disease, a genetic disorder of biliary copper excretion, may cause elevated aminotransferase levels in patients with no other symptoms of the disease. The clinical onset is usually between the ages of 5 and 25 years, but the diagnosis should be considered in patients up to the age of 40 years. The initial screening test for Wilson's disease is measurement of serum ceruloplasmin (Table 2). The levels will be reduced in approximately 85 percent of affected patients. Patients should also be examined by an ophthalmologist for Kayser–Fleischer rings.

If the ceruloplasmin level is normal and Kayser–Fleischer rings are absent, but the physician still suspects that Wilson's disease may be present, the next test is a 24-hour urine collection for a quantitative assessment of copper excretion. Excretion of more than 100 μg of copper per day is suggestive of Wilson's disease. The diagnosis is usually confirmed by liver biopsy to measure hepatic copper levels. Patients with Wilson's disease have hepatic copper levels of more than 250 μg per gram of liver, dry weight. Although the gene responsible for Wilson's disease has been identified, the number of disease-specific mutations is so great that molecular diagnosis is not yet feasible.

Alpha$_1$-Antitrypsin Deficiency

Alpha$_1$-antitrypsin deficiency is an uncommon cause of chronic liver disease in adults. Decreased levels of alpha$_1$-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. In affected patients, however, serum levels of alpha$_1$-antitrypsin may be increased in response to inflammation, causing a false negative result. The diagnosis is best established by phenotype determination.

Nonhepatic Causes

In a recent study, occult celiac sprue was the cause of chronically elevated aminotransferase levels in 13 of 140 asymptomatic patients who were referred for this reason to a liver clinic.[23] The diagnosis was made by measuring serum levels of antigliadin and antiendomysial antibodies. None of these patients had primary biliary cirrhosis, a liver disease that is occasionally found in patients with celiac sprue. On the basis of this study, we recommend testing for occult celiac sprue if other, more common causes of elevated aminotransferase levels have been ruled out (Table 2).

Elevated serum aminotransferase levels, especially aspartate aminotransferase levels, may be caused by disorders that affect organs or tissues other than the liver, with the most common being striated muscle. Conditions or activities that can cause such elevations include subclinical inborn errors of muscle metabolism; acquired muscle disorders, such as polymyositis; and strenuous exercise, such as long-distance running. If striated muscle is the source of increased aminotransferase levels, serum levels of creatine kinase and aldolase will be elevated to the same degree or to an even higher degree. Creatine kinase or aldolase levels should be measured if other, more common hepatic conditions have been ruled out (Table 2).

If, despite comprehensive testing as outlined in Ta-

ble 2, the cause of the elevation in aminotransferase levels remains unidentified, then a percutaneous liver biopsy may be indicated. If the alanine aminotransferase and aspartate aminotransferase levels are less than twice the normal value and no chronic liver condition has been identified, we recommend observation alone. Supporting this position are the results of two recent studies. The first study suggested that close clinical follow-up is the most cost-effective strategy for asymptomatic patients with negative tests for viral, metabolic, and autoimmune markers of liver disease and chronically elevated aminotransferase levels.[24] The second study examined 36 patients with a chronic elevation (at least 50 percent above normal) of alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase levels.[25] Patients with strong evidence of a particular liver disease were excluded. All patients underwent liver biopsy. The results of liver biopsy led to a change in the diagnosis in only five patients and to a change in treatment in two patients.

If the alanine aminotransferase and aspartate aminotransferase levels are persistently more than twice the normal value, we recommend a biopsy. Although the results of the biopsy are unlikely to lead to a diagnosis or to changes in management, they often provide reassurance to the patient and the physician that no serious disorder is present.

CAUSES OF ELEVATED ALKALINE PHOSPHATASE LEVELS

Elevations in serum alkaline phosphatase levels originate predominantly from two sources, liver and bone.[1] Women in the third trimester of pregnancy have elevated serum alkaline phosphatase levels because of an influx of placental alkaline phosphatase into their blood. In persons with blood type O or B, serum alkaline phosphatase levels may increase after the ingestion of a fatty meal, because of an influx of intestinal alkaline phosphatase. There are also reports of a benign familial elevation in serum alkaline phosphatase levels because of increased levels of intestinal alkaline phosphatase. Alkaline phosphatase levels also vary with age. Rapidly growing adolescents can have serum alkaline phosphatase levels that are twice those of healthy adults as a result of the leakage of bone alkaline phosphatase into blood. Also, serum alkaline phosphatase levels normally increase gradually between the ages of 40 and 65 years, particularly in women. The normal alkaline phosphatase level in an otherwise healthy 65-year-old woman is more than 50 percent higher than the level in a healthy 30-year-old woman.[26]

The first step in the evaluation of an elevated alkaline phosphatase level in a patient with no other symptoms is to identify the source of the elevation. Although electrophoretic separation on either polyacrylamide gel or Sepharose columns is the most sensitive and specific way of doing this, neither method is widely available.[1] If gel electrophoresis is not available, measurement of either serum 5′-nucleotidase or γ-glutamyltransferase should be performed. Levels of these enzymes are usually elevated in parallel with the elevation in the alkaline phosphatase level in patients with liver disorders, but they are not increased in patients with bone disorders. The finding of an elevated serum alkaline phosphatase level but a normal 5′-nucleotidase or γ-glutamyltransferase level should prompt an evaluation for bone diseases. Tests involving heat and urea denaturation of serum alkaline phosphatase are still used by many laboratories but are neither sensitive nor specific.

If the excess alkaline phosphatase is determined to be of liver origin and persists over time, the patient should be evaluated for chronic cholestatic or infiltrative liver diseases. Cholestatic diseases or conditions include partial obstruction of bile ducts, primary biliary cirrhosis, primary sclerosing cholangitis, adult bile ductopenia, and cholestasis induced by the use of drugs such as anabolic steroids. Infiltrative diseases include sarcoidosis, other types of granulomatous diseases, and less often, unsuspected metastasis of cancer to the liver. The appropriate initial tests are ultrasonography of the right upper quadrant to assess the hepatic parenchyma and bile ducts and serologic tests for antimitochondrial antibodies. The presence of antimitochondrial antibodies is highly suggestive of the presence of primary biliary cirrhosis. A finding of biliary dilatation suggests the presence of obstruction of the biliary tree. This finding is unlikely in the absence of hyperbilirubinemia. Should biliary dilatation or choledocholithiasis be present, endoscopic retrograde cholangiopancreatography is necessary to identify the cause of obstruction and can also be used to remove a stone or place a stent if required. Patients with serum antimitochondrial antibodies should undergo liver biopsy to confirm the diagnosis of primary biliary cirrhosis.

If the serologic test for antimitochondrial antibodies is negative and ultrasonography reveals no abnormality, but the alkaline phosphatase level remains more than 50 percent above the normal level, we suggest a liver biopsy and either endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography. If the increase in the alkaline phosphatase level is less than this, the results of all the other liver-enzyme tests are normal, and the patient has no symptoms, we suggest observation alone. This position is supported by the results of a recent study.[25]

CAUSES OF ELEVATED γ-GLUTAMYLTRANSFERASE LEVELS

γ-Glutamyltransferase is found in hepatocytes and biliary epithelial cells. Measurement of serum γ-glutamyltransferase provides a very sensitive indicator of

the presence or absence of hepatobiliary disease, but the usefulness of this test is limited by its lack of specificity. Elevated levels of γ-glutamyltransferase have been reported in a wide variety of clinical conditions, including pancreatic disease, myocardial infarction, renal failure, chronic obstructive pulmonary disease, diabetes, and alcoholism.[27] High serum γ-glutamyltransferase levels are also found in patients who are taking medications such as phenytoin and barbiturates.[28]

Some have advocated the use of serum γ-glutamyltransferase measurements to identify patients with unreported alcohol use. The reported sensitivity of an elevated γ-glutamyltransferase level for detecting alcohol ingestion has ranged from 52 to 94 percent.[29,30] Its lack of specificity makes the use of this test for this purpose questionable. In our opinion, measurement of serum γ-glutamyltransferase is best used as a way of evaluating the meaning of elevations in other serum enzyme levels. For instance, it can be used to confirm the hepatic origin of elevated alkaline phosphatase levels or to support the diagnosis of alcohol abuse in a patient with an elevated aspartate aminotransferase level and an aspartate aminotransferase:alanine aminotransferase ratio of at least 2:1.

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