

Evaluation of Abnormal Liver Tests

Fedja A. Rochling, MD

Assistant Professor of Medicine
Division of Gastroenterology and Hepatology
University of Arkansas for Medical Sciences and
Central Arkansas Veterans Healthcare System
Little Rock, Arkansas

Serum liver tests are important but often problematic in evaluating patients with and without symptoms of hepatic disease. The common term “liver function tests” is misleading because most tests used in clinical practice measure hepatocellular damage not function. True liver function tests are those that measure synthesis of proteins made by the liver (albumin, clotting factors) or the liver’s capacity to metabolize drugs. A commonly ordered panel of automated tests includes bilirubin, aminotransferases, alkaline phosphatase, and γ -glutamyl transpeptidase. This article reviews patterns of elevated enzyme values encountered in liver diseases and their diagnostic limitations and provides an algorithm for evaluating abnormal liver test results.

EVALUATION

Although as many as 6% of normal asymptomatic people may have abnormal liver enzyme levels, the overall prevalence of liver disease in the general population is only ~1%. Inherent to the definition of “normal range,” 5% of all test results from normal persons fall outside this range; hence, some abnormal liver tests are not truly abnormal. A practical approach to an isolated elevation of an aminotransferase level is to repeat the test, with further evaluation only if >2-fold elevation persists (**Table I**).

Initial evaluation of the patient with abnormal liver test results should include a physical examination and the patient’s history with an emphasis on risk factors for viral hepatitis, medication used in the preceding 6 months, consumption of herbal and alternative remedies, and occupational exposure to toxins. Liver disease may exist even in the absence of obvious risk factors. **Figure 1** shows an approach to the evaluation of asymptomatic patients with an abnormal liver test. Management of abnormal liver tests in the absence

of liver risk factors should involve repeating the test once. Risk factors or underlying conditions such as viral hepatitis, autoimmune hepatitis, hemochromatosis, Wilson’s disease (WD), α_1 -antitrypsin deficiency, and medications should have been excluded. If continued elevation of the enzyme values of >2 x the upper limit of normal for the reference laboratory is encountered, then further diagnostic evaluation with imaging studies and a liver biopsy is indicated. Recent publications point to the role of chemical agents such as dimethylformide, hydrazine derivatives, and hydrochlorofluorocarbons as etiologic agents for the development of abnormal liver blood tests in otherwise healthy individuals.

Bilirubin Levels

Normal serum bilirubin values represent a balance between production (degradation of hemoglobin) and hepatic elimination. Normal total serum bilirubin levels are <1.1 mg/dL, of which 70% is unconjugated (indirect) bilirubin.

TABLE I.

REFERENCE VALUES FOR LIVER TESTS

<i>Laboratory Test (Serum)</i>	<i>Range (Conventional Units)</i>
Alanine aminotransferase	1–45 U/L
Aspartate aminotransferase	1–36 U/L
Alkaline phosphatase	
Adult	35–150 U/L
Adolescent	100–500 U/L
Child	100–350 U/L
Bilirubin	
Conjugated	0.1–0.4 mg/dL (1.7–6.8 mmol/L*)
Total	0.3–1.1 mg/dL (5.1–19.0 mmol/L*)

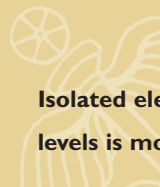
*International system of units. Normal values may vary in different clinical laboratories. Adapted from Borer WZ. Reference intervals for the interpretation of laboratory tests. In: Rakel RE, ed. *Conn's Current Therapy*. Philadelphia, Pa: WB Saunders Co; 1996:1197–1198.

In Gilbert syndrome (GS), or familial non-hemolytic hyperbilirubinemia, a genetic mutation causes impaired bilirubin glucuronidation. Glucuronidation involves the addition of glucuronic acid molecules to one or both bilirubin propionic acid moieties, thus resulting in the more polar and hence soluble bilirubin monoglucuronide or bilirubin diglucuronide. These steps are catalyzed by hepatic uridine diphosphate-glucuronosyltransferases (UGTs). This polymorphism may be present in ≤13% of whites. Its prevalence in other populations is unclear. The only significant abnormality in GS is mild unconjugated hyperbilirubinemia, which usually fluctuates between 2 and 5 mg/dL (34 to 86 μmol/L). Overt jaundice may be precipitated by systemic illness, starvation, stress, and altered drug metabolism. Hemolysis is excluded by the absence of anemia and reticulocytosis. Although liver histology in GS patients is normal, liver biopsy is not required for diagnosis.

GS is a benign condition that can be diagnosed only by excluding other causes of elevated bilirubin values or liver disease. In patients with GS who are exposed to acetaminophen, a subgroup exists that experiences less glucuronidation and more oxidation, thus raising the potential for acetaminophen-induced hepatotoxicity.

Adverse effects of anticancer agents have been observed in GS patients with metastatic colon cancer who received irinotecan (CPT-11), which is the semisynthetic analogue of the cytotoxic alka-

loid camphothecin (CPT). CPT-11 undergoes biotransformation to the active metabolite SN-38 (7-ethyl-10-hydroxycamphothecin). SN-38 undergoes significant biliary excretion by hepatic UGTs and enterohepatic circulation to form the SN-38 glucuronide, which is inactive and undergoes biliary excretion. The major dose-limiting toxicity of CPT-11 is diarrhea and myelosuppression. The diarrhea is likely due to the active metabolite SN-38, and the differential glucuronidation of SN-38 to SN-38G by hepatic UGTs could explain the variation seen in toxicities in CPT-11 recipients. In the future, polymerase chain reaction methods for the rapid and reliable identification of GS gene polymorphism may facilitate diagnosis and avoid more costly evaluation.



KEY POINT

Isolated elevation of unconjugated bilirubin levels is most likely caused by GS.

Other causes of elevated bilirubin levels are shown in **Table II**. There is considerable overlap in the range of elevated bilirubin values observed in these conditions. Fractionation of conjugated and unconjugated bilirubin does not distinguish between parenchymal (hepatocellular) and obstructive (cholestatic) jaundice. Nevertheless, hemolysis

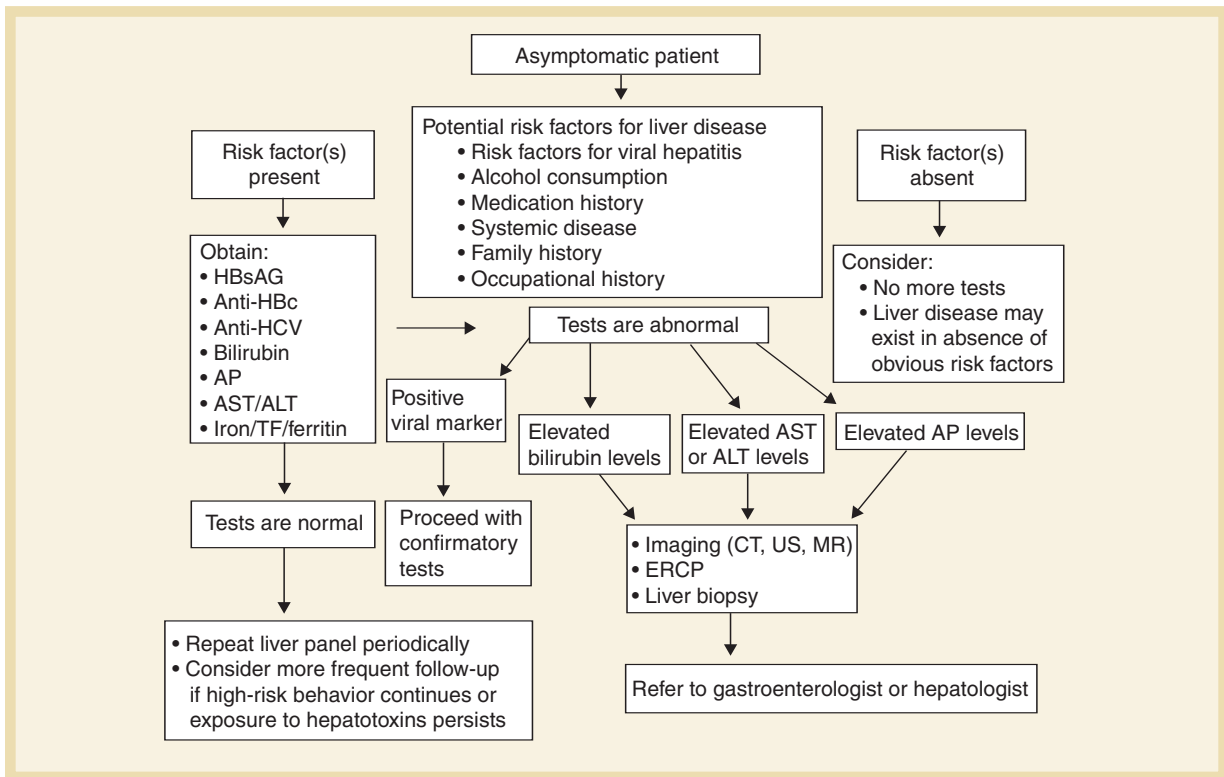


Figure 1. Suggested approach to using liver tests to evaluate asymptomatic patients. HBsAg = hepatitis B surface antigen; anti-HBc = antibody to hepatitis B core antigen; anti-HCV = antibody to hepatitis C virus; AP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; TF = transferrin; CT = computed tomography; US = ultrasound; MR = magnetic resonance; ERCP = endoscopic retrograde cholangiopancreatography. Modified from Bach N, Koff RS, Maddrey W. When and how to screen for liver disease. *Intern Med.* 1999;20:49, with permission.

alone rarely raises serum bilirubin levels >6 mg/dL. In complete bile duct obstruction, the maximum observed bilirubin level is ~30 mg/dL because the kidneys continue to excrete conjugated bilirubin.

Bilirubin levels of 25 to 30 mg/dL indicate severe hepatic parenchymal disease associated with hemolysis or renal disease (Table III). History, physical examination, and imaging studies such as transabdominal ultrasonography are needed to further determine the cause of jaundice. The threshold value of the serum bilirubin associated with jaundice is variable, but in general icterus is clinically detectable at 2 to 3 mg/dL.

Serum Aminotransferases

Serum aminotransferases are enzymes that act as sensitive indicators of hepatocellular damage. The less specific aspartate aminotransferase (AST) is localized in heart, skeletal muscle, kidney, brain,

pancreas, lungs, leukocytes, and erythrocytes. Alanine aminotransferase (ALT) is limited to the liver.

Aminotransferase levels are elevated in acute and chronic hepatitis, cirrhosis, hepatic congestion, and infiltrative diseases such as infection or cancer (Table IV). The degree of enzyme level elevation does *not* correlate with eventual outcome, even when aminotransferase values reach the several thousands range. In contrast, patients with acute alcoholic hepatitis may have severe liver dysfunction despite elevated aminotransferase levels only in the 200 to 400 IU/L range. In drug toxicity or acute viral hepatitis, a full recovery is usually seen. Declining AST and ALT levels generally indicate recovery; however, although rare, a rapid decline may portend a poor outcome because of mass hepatocyte death. In some patients a rapid decline of transaminases may be accompanied by a progres-

TABLE II.

CAUSES OF INCREASED SERUM BILIRUBIN LEVELS

<i>Unconjugated</i>	<i>Conjugated</i>
<ul style="list-style-type: none"> ● Hemolysis ● Immature enzyme systems <ul style="list-style-type: none"> – Physiologic jaundice of newborn – Jaundice of prematurity ● Inherited defects <ul style="list-style-type: none"> – Gilbert syndrome – Crigler-Najjar syndrome ● Drug effects 	<ul style="list-style-type: none"> ● Hepatocellular disease <ul style="list-style-type: none"> – Cirrhosis – Hepatitis – Drugs ● Intrahepatic cholestasis <ul style="list-style-type: none"> – Drugs – Pregnancy ● Benign postoperative jaundice ● Sepsis ● Congenital hyperbilirubinemia <ul style="list-style-type: none"> – Dubin-Johnson syndrome – Rotor’s syndrome ● Obstructive jaundice <ul style="list-style-type: none"> – Extrahepatic – Intrahepatic

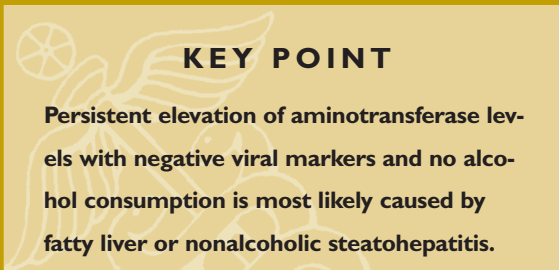
Adapted from Friedman LS, Martin P, Munoz SJ. Liver function tests and the objective evaluation of the patient with liver disease. In: Zakim D, Boyer TD, eds. *Hepatology: A Textbook of Liver Disease*. 3rd ed. Philadelphia, Pa: WB Saunders Co; 1996:791–833.

sive coagulopathy, hypoglycemia, and infection, thus resulting in death.

In alcoholic liver disease, ALT levels tend to be normal or minimally elevated. The AST to ALT ratio is useful diagnostically in patients with alcoholic liver disease, 70% of whom have a ratio >2. Low AST levels may be seen in hemodialysis and pyridoxine-deficient patients.

Isolated, persistently elevated aminotransferase levels, with negative viral markers and an

Elevation of immunoglobulin (Ig)-complexed AST levels (“macro-AST”) detected on routine blood testing may falsely imply hepatic dysfunction. The elevated AST values can persist for many years. Liver and muscle disease can be excluded by the finding of normal serum levels of ALT and creatine phosphokinase. Evaluation for a macroenzyme should be pursued only when a single enzyme level is elevated and more common causes of abnormal liver test results have been excluded. The presence of macro-AST can be determined by exclusion chromatography, electrophoresis, activation assays with pyridoxal-5’-phosphate, or measurement of urinary excretion. No literature is available that describes one methodology as preferable to another.



KEY POINT

Persistent elevation of aminotransferase levels with negative viral markers and no alcohol consumption is most likely caused by fatty liver or nonalcoholic steatohepatitis.

absence of alcohol abuse, usually signify fatty liver or nonalcoholic steatohepatitis. Initially, when an isolated elevation of an aminotransferase level is reported, the test should be repeated. Further evaluation is indicated only if a persistent, >2-fold elevation is observed.

Alkaline Phosphatase

Alkaline phosphatase (AP) comprises a family of enzymes located in liver, bone, placenta, and intestine that hydrolyze phosphate esters at alkaline pH. In healthy subjects, circulating AP is derived from bone and liver; in those with blood group O, AP is primarily of intestinal origin. There is a direct correlation between serum AP levels and body weight and frequency of cigarette smoking and an indirect correlation with height.

TABLE III.

CLINICAL APPROACH TO THE PATIENT WITH JAUNDICE

Diagnostic Factors	Type of Jaundice			
	Hemolytic	Hepatocellular	Intrahepatic Cholestatic	Extrahepatic Cholestatic
Symptoms	May be asymptomatic or backache, joint pain	Nausea, vomiting, fever, anorexia	Deep jaundice, dark-colored urine, light-colored stools, pruritus	Deep jaundice, dark-colored urine, light-colored stools, pruritus cholangitis, biliary colic
Physical findings	Splenomegaly	Tender hepatomegaly,* splenomegaly	Tender hepatomegaly	Hepatomegaly, palpable gallbladder
Liver tests				
Bilirubin				
Total	<6 mg/dL	Variable	Variable, may be >30 mg/dL	<30 mg/dL
Direct	<20%	>50%	>50%	>50%
Alanine aminotransferase	Normal	>5-fold increase	2- to 5-fold increase	<2- to 3-fold increase; >3- to 5-fold increase with cholangitis
Alkaline phosphatase	Normal	<2- to 3-fold increase	>3- to 5-fold increase	>3- to 5-fold increase
Prothrombin time	Normal	Prolonged	Prolonged	Prolonged
Corrected by vitamin K	–	No	Variable	Yes
Ultrasonography of liver				
Biliary dilatation	No	No	No	Yes
Endoscopic retrograde cholangiopancreatography	Not necessary	Not necessary	Usually not necessary	Usually necessary

*May or may not be present. Reprinted with permission from Kamath PS. Clinical approach to the patient with abnormal liver test results. *Mayo Clin Proc.* 1996;71:1089–1095.

In the third month of pregnancy, AP levels are elevated to 2 × the upper limit of normal. Other extrahepatic causes of elevated AP levels include hyperthyroidism, cardiac failure, lymphoma, hypernephroma, and Paget's disease of the bone. Infiltrative or granulomatous hepatic disease such as tuberculosis, sarcoidosis, fungal infections, and lymphoma can elevate AP levels disproportionately to bilirubin.

Determining whether an isolated elevation of AP levels indicates liver or biliary disease can be approached by electrophoretic fractionation of AP

or by measurement of γ -glutamyl transpeptidase (GGT), 5' nucleotidase, or leucine aminopeptidase. In nonpregnant patients, increased GGT levels indicate that the elevated AP levels are of hepatic origin. In \leq one third of cases, elevated levels of hepatic AP are nonspecific. The degree of elevation of AP levels does not help differentiate between extrahepatic and intrahepatic cholestasis.

Low to undetectable levels of AP can be seen in fulminant WD, hypothyroidism, pernicious anemia, congenital hypophosphatasia, zinc deficiency, and in blood samples anticoagulated with oxalo-

TABLE IV.

TYPICAL RANGE OF ELEVATED AMINOTRANSFERASE LEVELS (AST AND ALT) IN VARIOUS LIVER DISEASES

Mild Elevation (<3-fold)

- Fatty liver
- Nonalcoholic steatohepatitis
- Chronic viral hepatitis

Moderate Elevation (3- to 20-fold)

- Acute viral hepatitis
- Chronic viral hepatitis
- Alcoholic hepatitis
- Autoimmune hepatitis

Severe Elevation (>20-fold)

- Viral hepatitis
- Drug- or toxin-induced hepatitis
- Ischemic hepatitis

AST = aspartate aminotransferase; ALT = alanine aminotransferase.

acetate. **Figure 2** provides an evaluation approach for elevated AP levels.

γ -Glutamyl Transpeptidase

Elevation of GGT levels may be associated with liver, biliary or pancreatic disease, myocardial infarction, renal disease, chronic lung disease, and diabetes. Elevation of GGT levels is a sensitive but nonspecific indicator of biliary disease. The major use of GGT is to confer additional liver specificity in evaluating elevated AP levels.

GGT, a microsomal enzyme, provides an indirect but nonspecific approach to assessment of mixed-function oxidase activity, including cytochrome P-450. Agents such as ethanol and phenytoin, which induce these enzymes, cause elevation of GGT levels.

In a large study conducted in Norway, GGT levels were measured in >21,000 healthy people. A sex-specific multiple regression analysis showed a strong association between GGT levels and body mass index, alcohol use, and total serum cholesterol and a somewhat weaker association with serum triglycerides, high-density lipoprotein cholesterol, heart rate, blood pressure, use of analgesics, and time since last meal. The association of high levels of GGT (and other liver enzymes) with moderate obesity in nonalcoholic, nondrinking men has been attributed to hepatic steatosis.

Familial idiopathic elevation of GGT levels has been reported and should be considered only when other common causes of elevated GGT levels have been excluded.

TESTS OF LIVER FUNCTION

Although the tests discussed earlier are often termed “liver function tests,” the term is a misnomer; most liver tests used in clinical practice measure hepatocellular damage rather than liver function. True liver function tests measure the liver’s synthesis of proteins (albumin, clotting factors) or its capacity to metabolize drugs (galactose or aminopyrine clearance). The latter are rarely used in general practice and are not reviewed here.

Albumin

Measurement of serum albumin levels is useful in chronic liver disease and is a component of grading systems (eg, Childs-Turcotte-Pugh, Mayo Endstage Liver Disease Score). The protein is not a good indicator of hepatic synthetic function in acute liver disease due to its half-life of 20 days. The patient with alcoholic liver disease, protein malnutrition, or chronic hepatitis may experience downregulation of albumin synthesis. Patients with ascites may have upregulated albumin synthesis but exhibit low serum levels due to the larger volume of distribution.

Prothrombin Time

Prothrombin time (PT), a universal indicator of liver failure, is prolonged in cholestasis or severe hepatocellular disease. Correction of the PT after parenteral administration of vitamin K may help distinguish cholestasis from hepatocellular disease. (When the PT is prolonged, vitamin K is given 5 to 10 mg/d for ≤ 3 days; if the PT improves by 30% or

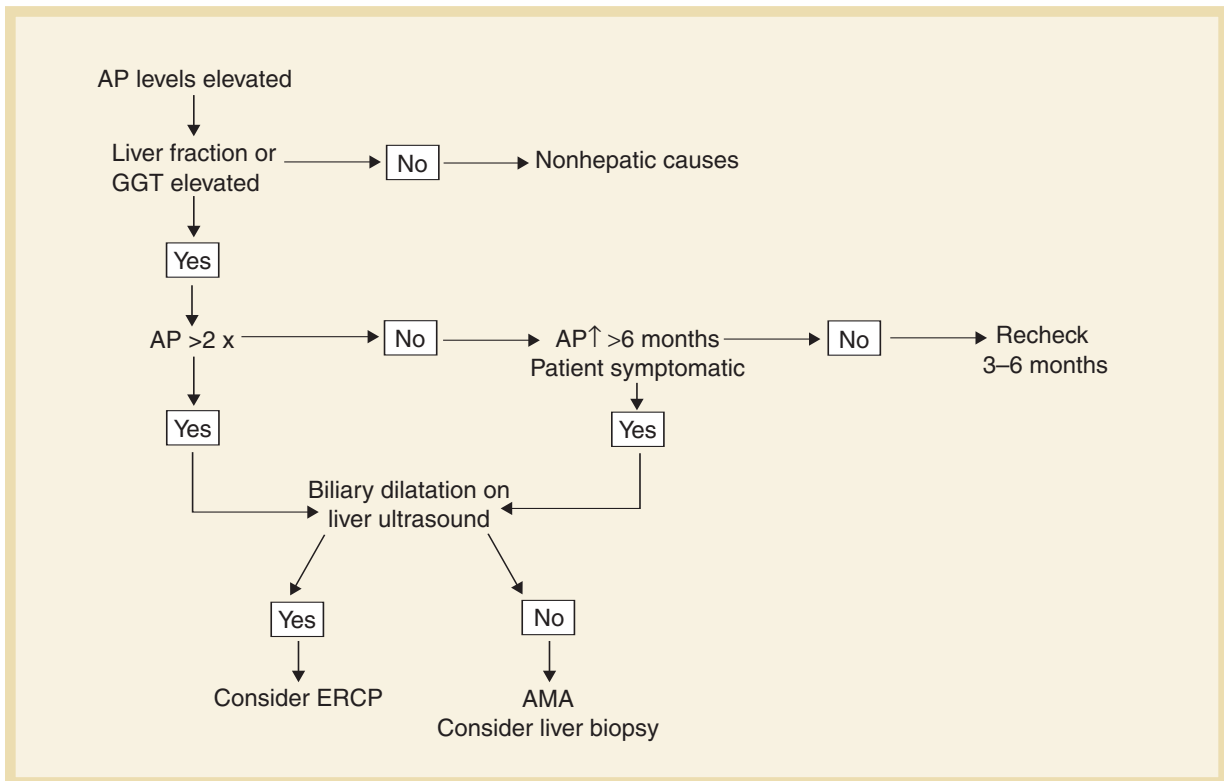


Figure 2. Approach to elevation of alkaline phosphatase (AP) levels. GGT = γ -glutamyl transpeptidase; ERCP = endoscopic retrograde cholangiopancreatography; AMA = antimitochondrial antibody. From Kamath PS. *Clinical approach to the patient with abnormal liver test results.* Mayo Clin Proc. 1996;71:1089–1095, with permission.

normalizes within 24 hours of vitamin K administration, then hepatic function is intact with regard to clotting factor production and PT prolongation was probably due to vitamin K deficiency.)

In acetaminophen-induced fulminant hepatic failure, PT is an important early predictor of outcome and may assist with timely referral to a liver transplant facility. Due to variability among thromboplastin reagents, there are large interlaboratory differences in PT results. Nevertheless, PT standardization in patients with liver failure using the international normalized ratio (INR) has been mis-

leading. Some authorities discourage the use of INR to assess prognosis in hepatic failure.

Immunoglobulins

Individuals with cirrhosis may demonstrate elevated levels of Igs due to impaired function of the hepatic reticuloendothelial system (Kupffer's cells) and portovenous shunting of blood. Various diseases are associated with distinctive Ig patterns. The pattern of Igs in antimitochondrial antibody (AMA)-positive primary biliary cirrhosis (PBC) is characterized by elevated IgM levels with normal IgA levels. In rare cases of AMA-negative PBC, IgG levels are elevated whereas IgM levels are usually normal.

Persistent hypergammaglobulinemia suggests chronic active hepatitis, usually due to an autoimmune etiology. In autoimmune hepatitis, the response to immunomodulatory therapy can be monitored by following serum aminotransferase levels and quantitative Ig values.

KEY POINT

In acetaminophen-induced fulminant hepatic failure, PT is an important early predictor of outcome and may assist with timely referral to a liver transplant facility.

TABLE V.

AGENTS REPORTED TO CAUSE ELEVATIONS IN LIVER ENZYME LEVELS

Medications	Herbs and Alternative Remedies	Substances of Abuse and Toxins
<ul style="list-style-type: none"> • Antibiotics • Antiepileptic drugs • HMG-CoA reductase inhibitors • Sulfonylureas • NSAIDs 	<ul style="list-style-type: none"> • Chaparral • Chinese herbs • Gentian • Scutellaria (skullcap) • Germander • Alchemilla • Senna • Shark cartilage 	<ul style="list-style-type: none"> • Anabolic steroids • Cocaine • 5' Methoxy-3,4 methylenedioxy • Methamphetamine hydrochloride (Ecstasy) • Phencyclidine hydrochloride (angel dust) • Glues and solvents containing toluene • Trichloroethylene, chloroform • <i>Amanita phalloides</i> toxin

HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; NSAIDs = nonsteroidal anti-inflammatory drugs. Modified from Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N Engl J Med.* 2000;342:1266–1271, with permission.

KEY POINT

In autoimmune hepatitis, continued evaluation of serum aminotransferase levels and quantitative Ig values is an effective way to monitor response to immunomodulatory therapy.

Drug- and Toxin-Induced Elevation of Liver Enzyme Levels

Many drugs and industrial toxins affect the liver and cause either hepatocellular or cholestatic injury, as evidenced by elevated liver enzyme levels (Table V). Drug-induced liver injury accounts for >30% of acute liver failure and 2% to 20% of hospitalized jaundiced patients. Monitoring both ALT and AST levels is recommended for drugs with hepatotoxic potential. ALT level elevations <3 x the upper limit of normal require weekly follow-up. Drugs should be discontinued immediately when ALT levels exceed 3 x the upper limit of normal.

LIMITATIONS OF LIVER TESTS

Commonplace errors in the interpretation of liver test results may occur in the following situations:

Workup for isolated elevated bilirubin levels.

Costly and unnecessary testing may be pursued in patients who have intermittent jaundice with isolated unconjugated hyperbilirubinemia. The most likely diagnosis in this setting is GS; correctly establishing this diagnosis can defer the need for further workup.

Normal aminotransferase levels in established cirrhosis. Patients with compensated or decompensated cirrhosis may have entirely normal or even low-normal aminotransferase levels, thus falsely reassuring patient and physician. In fact, such patients with hepatitis C-related cirrhosis may have active hepatitis and may benefit from antiviral therapy, prophylaxis for esophageal variceal bleeding with β-blockers, or other interventions.

Rapidly falling aminotransferase levels in acetaminophen-induced hepatic failure. The rapid rise and fall of AST and ALT levels in acetaminophen- or toxin-induced hepatic failure may be falsely reassuring. The patient may be developing fulminant hepatic failure with hyperbilirubinemia, coagulopathy, hypoglycemia, and multisystem organ failure. In this setting, it is important to establish the timeline of ingestion or exposure, closely follow clinical progress, and initiate timely referral to

KEY POINT

Drug-induced liver injury accounts for >30% of acute liver failure and ≤20% of hospitalized jaundiced patients. Monitoring aminotransferase levels is recommended for drugs with hepatotoxic potential. ALT level elevations <3 X the upper limit of normal require weekly follow-up, and drugs should be discontinued at ALT level elevations >3 X upper normal limits.

a transplant center. The clinician should not rely on “improving” aminotransferase values.

AST and ALT levels in the 200 to 400 IU/L range in severe alcoholic hepatitis. In the absence of concurrent acetaminophen ingestion, the AST and ALT levels in individuals with alcoholic hepatitis rarely rise above 7 x the upper limit of normal. Nevertheless, there may be severe hepatocellular injury resulting in clotting abnormalities, hypoglycemia, synthetic dysfunction, multiorgan failure, and death.

GENETIC TESTING IN ADULT LIVER DISEASE

Hereditary hemochromatosis (HH) affects 1:300 individuals. Approximately 80% of cases result from a mutation in the hemochromatosis (*HFE*) gene. A homozygous missense *HFE* mutation, cysteine to tyrosine at position 282, is found in >80% of phenotypic HH patients. HH should be suspected when patients present with symptoms or physical findings such as abnormal liver enzymes, a family history of HH, or abnormal iron studies indicative of liver disease.

Early diagnosis and treatment reduce morbidity and mortality. However, serum iron studies are associated with false-positive and false-negative results. Reliance on these alone to diagnose HH can be misleading. *HFE* gene testing is a reasonable step after repeat-fasting elevated transferrin levels (>50%) or elevated serum ferritin levels

(>500 μg/L). However, ≤20% of patients with clinical HH do *not* have *HFE* mutations.

For the individual <40 years of age with normal aminotransferase levels, an elevated transferrin level and a detectable *HFE* mutation establish the diagnosis of HH and no liver biopsy is needed. If transferrin levels are elevated and genetic testing is negative, the next step is quantitative hepatic iron determination.

WD occurs in 1:30,000 to 1:50,000 persons with a gene frequency of 1:90 to 1:150. In WD, a defect in copper homeostasis results in copper accumulation due to reduced biliary excretion. The WD gene is located on chromosome 13 and has been designated *ATP7B*. More than 60 polymorphisms of the WD gene have been described. The most common mutation, histidine to glutamine at position 1069, is present in 30% of WD patients of European ancestry. Genetic testing has not been useful in clinical practice due to multiple disease-specific mutations and the low prevalence of mutations in clinically phenotypic WD. Diagnosis of WD requires serum ceruloplasmin measurement, urinary copper determination, slit-lamp examination for the presence of Kayser-Fleischer rings, and quantitative hepatic copper determination.

SUMMARY

Management of the asymptomatic patient with a liver test abnormality is a frequent challenge of primary care. The abnormality may be a false-positive value or may indicate a disorder of bilirubin metabolism, acute hepatocellular disease, a cholestatic disorder, infiltrative diseases, or a chronic hepatocellular disorder. The commonly ordered set of tests includes bilirubin, aminotransferases, AP, and GGT. These tests should be done before ordering an invasive test such as liver biopsy.

SUGGESTED READING

Bach N, Koff RS, Maddrey W. When and how to screen for liver disease. *Intern Med.* 1999;20:49.

Bacon BR. Iron overload states. *Clin Liver Dis.* 1998; 2:63–75.

Borer WZ. Reference intervals for the interpretation of laboratory tests. In: Rakel RE, ed. *Conn's Current Therapy*. Philadelphia, Pa: WB Saunders Co; 1996:1197–1198.

Friedman LS, Martin P, Munoz SJ. Liver function tests and the objective evaluation of the patient with liver disease. In: Zakim D, Boyer TD, eds. *Hepatology: A Textbook of Liver Disease*. 3rd ed. Philadelphia, Pa: WB Saunders Co; 1996:791–833.

Gopal DV, Rosen HR. Abnormal findings on liver function tests. Interpreting results to narrow the diagnosis and establish a prognosis. *Postgrad Med*. 2000;107:100–114.

Johnston DE. Special considerations in interpreting liver function tests. *Am Fam Phys*. 1999;59:2223–2230.

Kamath PS. Clinical approach to the patient with abnormal liver test results. *Mayo Clin Proc*. 1996;71:1089–1095.

Kew MC. Serum aminotransferase concentration as evidence of hepatocellular damage. *Lancet*. 2000;355:591–592.

Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N Engl J Med*. 2000;342:1266–1271.

Pratt DS, Kaplan MM. Evaluation of the liver: laboratory tests. In: Schiff ER, Sorrell MF, Maddrey WC, eds. *Schiff's Diseases of the Liver*. 8th ed. Philadelphia, Pa: Lippincott Williams & Wilkins Inc; 1999:205–244.

Whitehead MW, Hawkes ND, Hainsworth I, Kingham JG. A prospective study of the causes of notably raised aspartate aminotransferase of liver origin. *Gut*. 1999;45:129–133.



Dialogue Box

ADVISORY BOARD

What is your management of the patient with a mild elevation, that is less than 2-fold, of AST and ALT levels?

RAUFMAN

In the asymptomatic patient I would repeat the test in 1 to 3 months. Since it is common in a patient with hepatitis C for serum transaminase levels to fluctuate back and forth from normal, I would also do a hepatitis C antibody test. If that test is negative and the ALT levels remain 2-fold or less elevated, I would check the levels again in 6 to 9 months. I definitely wouldn't ignore it, but I wouldn't feel compelled to evaluate the patient further. Sometimes you see patients who don't feel comfortable with this approach and have to know what the precise cause of the elevation is regardless of how mild the abnormality. In such a situation, you're going to have to decide whether a more aggressive diagnostic approach, possibly even a liver biopsy, is reasonable in an effort to allay the patient's anxiety.

ADVISORY BOARD

In a patient found to have an unconjugated hyperbilirubinemia, what is the minimum

workup required to make the diagnosis of GS?

RAUFMAN

Provided the patient is relatively young and the serum bilirubin level is no higher than 5 mg/dL, I would require only that the patient have normal liver tests, that is, normal transaminase levels and normal alkaline phosphatase levels, with no evidence of hemolysis or coagulopathy and a normal complete blood cell count. In the asymptomatic patient with normal liver tests, I would feel secure with the diagnosis and would simply follow the patient.

ADVISORY BOARD

What do you mean by "follow the patient"?

RAUFMAN

I would repeat the bilirubin test periodically, assuming this is a patient I see in practice, and tell the patient to call if any signs or symptoms of anything develop. I would then repeat the test in 1 or 2 months to make sure there was no upward trend. For example, if the bilirubin level went up and there was no evidence that the patient had been stressed, I would be more concerned about another cause for the increased bilirubin.

Dialogue Box

ADVISORY BOARD

What can be expected in a patient with GS subjected to the stress of the postoperative period?

RAUFMAN

For most patients, uncomplicated surgery should not make a difference if the patient is kept adequately hydrated and there isn't significant third-spacing of blood. A minor 1- to 2-mg/dL rise of bilirubin might be seen during the perioperative period, but that really shouldn't be a problem. The liver synthetic function in terms of clotting should remain perfectly normal.

ADVISORY BOARD

In the acute setting in the emergency room, if someone came in with a hepatocellular injury such as acute viral hepatitis, what parameters would you use to determine the severity and whether the patient requires admission?

RAUFMAN

I would evaluate several parameters. Findings that would warrant hospital admission include the presence of coagulopathy with a prolonged INR, mental status abnormalities suggesting hepatic encephalopathy, the presence of hypoglycemia, and, particularly with the patient with viral hepatitis, inability to tolerate oral intake, electrolyte abnormalities, or significant dehydration.

ADVISORY BOARD

In the workup of a patient with elevated ALT and AST levels, what laboratory tests do you order to exclude the possibility of autoimmune hepatitis?

RAUFMAN

I generally order the antinuclear antibody (ANA)

and anti-smooth muscle antibody tests. For the patient with whom I have a higher index of suspicion, for example a woman with rash and arthralgias, I would also order more specialized tests such as a liver-kidney microsomal antibody. Otherwise a normal ANA and normal smooth muscle antibody should rule out autoimmune hepatitis most of the time.

ADVISORY BOARD

In what settings would a patient likely be exposed to hepatotoxic chemicals such as dimethyl-fluoride hydralazine derivatives and hydrochlorofluorocarbons?

RAUFMAN

Situations where there is risk of exposure to industrial solvents. For example, patients involved in the dry cleaning business or who work as janitors can be exposed to fumes from these solvents and develop liver disease over time.

ADVISORY BOARD

What is the value of including the AST in the screening panel?

RAUFMAN

For detecting alcoholic liver disease. The ALT/AST ratio can be really helpful at times in discriminating alcoholic liver disease from other causes of elevated transaminase levels, such as viral hepatitis. Although the AST is nonspecific and can come from a lot of different organs, such as muscle, it can be of value as an early indicator of alcoholic liver disease.

ADVISORY BOARD

Do you think that AST is a better marker for alcoholic injury than the GGT?



Dialogue Box

RAUFMAN

Yes. They look at different things, but in terms of actual injury, the AST is better at detecting the development of alcoholic hepatitis. GGT levels do go up in alcoholic liver disease, but they also go up in other disease states such as cholestatic liver disease. I don't think GGT is as helpful as AST because it isn't quite as specific as we would like to think. I find the real value of the GGT to be in the workup of elevated AP levels—if the GGT levels are elevated then the elevated AP levels are likely hepatobiliary in origin; if they are normal, then the elevation is likely coming from bone.

ADVISORY BOARD

How do you screen for hemochromatosis?

RAUFMAN

I usually screen by ordering the transferrin saturation. If the iron saturation is <50%, that excludes hemochromatosis.

ADVISORY BOARD

What tests do you order to screen for WD?

RAUFMAN

I begin by ordering a serum ceruloplasmin. In interpreting the result, it is important to recognize that patients with WD can have a low-normal level in the range of 20 to 30 mg/dL and thus only a value that is above 30 mg/dL rules out WD. However, if your index of suspicion for WD is

high or if the patient presents a diagnostic enigma, the slit-lamp examination, a 24-hour urine collection for copper, and even a liver biopsy for copper content may be needed to more definitively exclude this metabolic disorder.

ADVISORY BOARD

Is there a role anymore for ordering a liver-spleen scan?

RAUFMAN

The liver-spleen scan is rarely if ever used. There is no indication for it. We used it in the past because no other imaging techniques were available. It is a very insensitive test, having its basis on technetium being picked up by the reticular endothelial system in the liver. Areas with no uptake suggested the presence of a mass lesion, but you really couldn't say much more than that. It has been effectively replaced by computed tomography or magnetic resonance imaging.

ADVISORY BOARD

Why is the presence of a persistent hypergammaglobulinemia of value in identifying patients with autoimmune hepatitis if it is also a finding in patients with end-stage liver disease regardless of cause?

RAUFMAN

Because the hypergammaglobulinemia is seen in patients with autoimmune hepatitis relatively early in the disease when they still have normal liver function and the sole manifestation of the disease is a mild elevation in transaminase levels.