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Abnormal liver test results on routine screening

How to evaluate, when to refer for a biopsy

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CME learning objectives

- To become familiar with various serologic liver tests and the indications for liver biopsy
- To understand how hepatitis and other chronic liver diseases affect the results of liver enzyme tests
- To be able to differentiate between alcohol-related liver disease and steatohepatitis unrelated to alcohol use

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Preview: Primary care physicians are often the first healthcare professionals to see abnormalities that show up in routine serum liver testing--results that may indicate liver disease. In this article, Drs Mallory, Lee, and Kowdley offer a practical approach to evaluating abnormal levels of markers of hepatocellular injury, cholestasis, and liver synthetic function. They also explore the considerations that might prompt physicians to request a liver biopsy.

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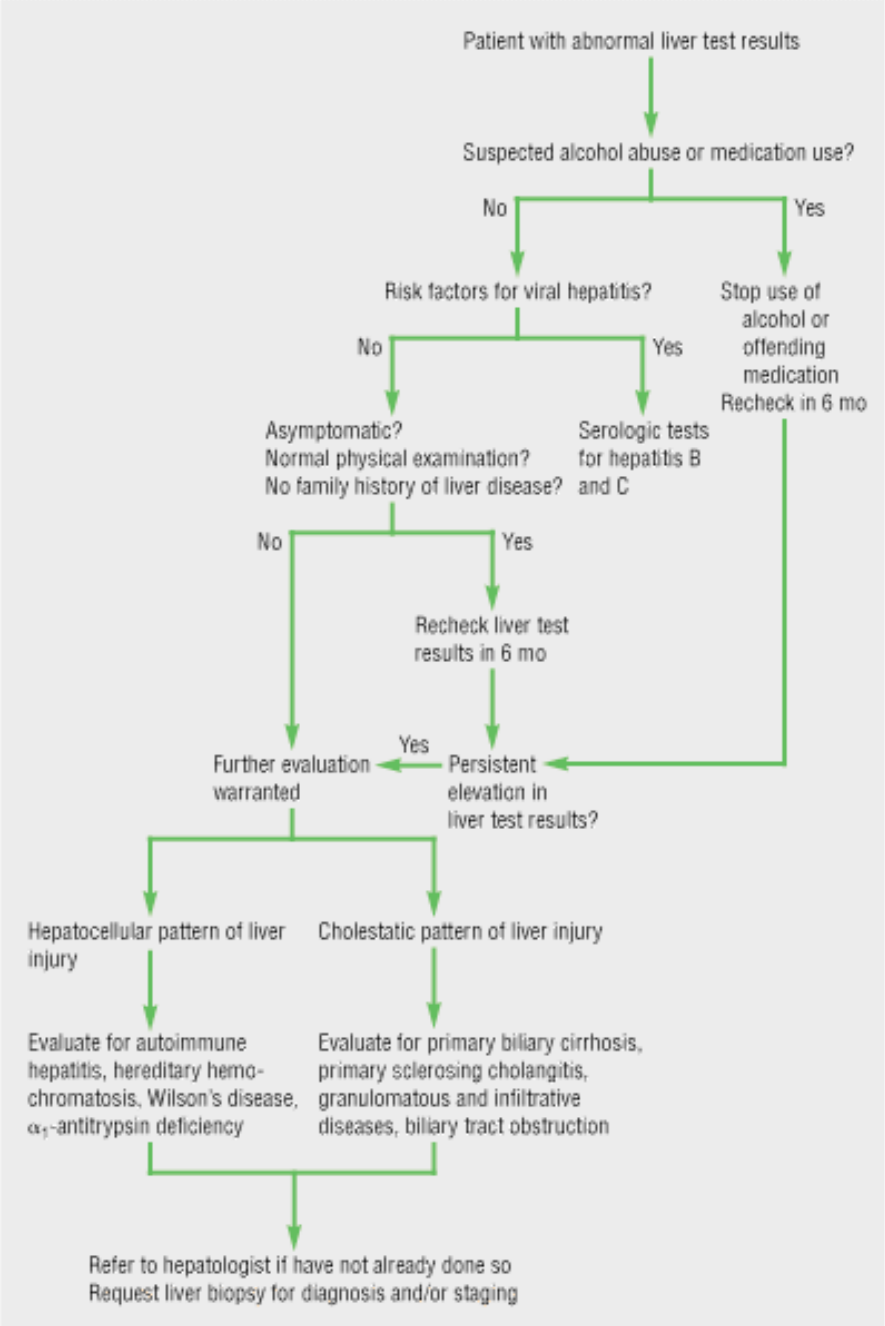
Serum liver biochemical studies are some of the tests most frequently ordered by primary care physicians, and abnormal results often lead to referral to a specialist. Abnormal results can be divided into three distinct categories: (1) markers of hepatocellular injury (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), (2) markers of cholestasis (alkaline phosphatase, 5'-nucleotidase, gamma-glutamyltransferase [GGT], and bilirubin), and (3) markers of liver synthetic function (albumin and prothrombin time).

Evaluation of abnormal results

The primary care physician is often the first healthcare professional to discover that a patient has abnormal liver test results. Serum liver tests are included in most automated blood chemistry panels and may be the first indication of liver disease. Figure 1 outlines a stepwise approach to the evaluation of abnormal liver test results.



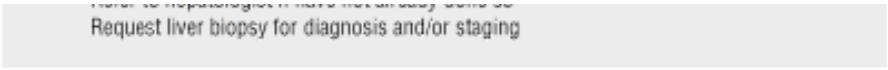


Figure 1. Algorithm for evaluation of abnormal liver test results.

The initial step in evaluating a patient with abnormal results is to repeat the tests. This is helpful both to confirm the test result and to evaluate the effect of first-line interventions, such as the discontinuation of hepatotoxic medications or alcohol. It is important to emphasize that in some liver diseases, such as chronic hepatitis C, serum liver enzyme levels can be intermittently or persistently normal. If a patient has risk factors for chronic liver disease (in particular, hepatitis B or C), the physician should proceed with further evaluation despite normal liver enzyme levels.

Medical history

A comprehensive medical history can help in the diagnosis of chronic liver disease. Symptoms such as fatigue, pruritus, and vague right upper-quadrant pain may be present. Other symptoms, such as sleep-wake reversal, memory or concentration difficulties, easy bruisability, or peripheral edema, suggest more advanced liver disease. Careful history taking may also provide clues to the possible cause of abnormal liver test results. It should involve a complete medication list, including over-the-counter and herbal preparations, because numerous medications can cause different patterns of abnormal liver test results (1) (table 1).

The US public increasingly uses herbal preparations in an effort to promote health. However, many of these compounds can have toxic effects on the liver, ranging from acute hepatitis to veno-occlusive disease. There are several reports of hepatotoxicity related to germander (*Teucrium chamaedrys*), jin bu huan, ma huang, chaparral (*Larrea tridentata*), mistletoe (*Viscum album*), and senna (*Cassia angustifolia*) (2). Because of the lack of prospective data about effects on the liver, the true incidence of hepatotoxicity related to herbal supplementation is unknown.

A patient's occupational history is also important in the evaluation of abnormal liver test results. Exposure to industrial solvents such as dimethylformamide, 2-nitropropane, 1,1,1-trichloroethane, and trichloroethylene may be associated with a hepatocellular pattern of injury. Methylene dianiline, an epoxy resin hardener, has been shown to cause cholestatic liver injury. Granulomatous hepatitis has been observed with beryllium and copper exposure, and hepatoportal sclerosis (noncirrhotic portal hypertension) has been described with exposure to vinyl chloride monomer, arsenic, and thorium.

Family history helps in the diagnosis of classic genetic diseases such as hemochromatosis, Wilson's disease, and alpha$_1$-antitrypsin deficiency. In addition, a genetic predisposition to such traits as obesity, type 2 diabetes mellitus, and hypertriglyceridemia is a recognized risk factor for nonalcoholic steatohepatitis (NASH) and cryptogenic cirrhosis.

A carefully taken social history, including high-risk habits and

other risk factors for viral hepatitis, is an important part of the patient encounter. The physician should always ask about the duration and amount of alcohol consumption, keeping in mind that patients sometimes feel compelled to minimize their alcohol history or deny alcohol use altogether.

Physical examination

The physical examination of a patient with abnormal liver test results should concentrate on signs suggestive of specific causes of liver disease and signs of decompensated cirrhosis (table 2). Alcoholic liver disease, hemochromatosis, and primary biliary cirrhosis are more commonly associated with hepatomegaly than are other diseases. Skin hyperpigmentation and arthralgias may be seen in hemochromatosis. Kayser-Fleischer rings and neurologic motor abnormalities can be seen in Wilson's disease. In the later stages of many different liver diseases, signs of cirrhosis may become evident. These include muscle wasting, jaundice, spider angiomas, palmar erythema, gynecomastia, testicular atrophy, ascites, asterixis, and splenomegaly.

Chronic liver diseases linked to hepatocellular injury

The following section reviews several important causes of hepatocellular injury. Other key causes of chronic hepatocellular disease, such as Wilson's disease and alpha$_1$-antitrypsin deficiency, are discussed elsewhere.

Hepatitis C

About 175 million people worldwide and 4 million people in the United States are infected with the hepatitis C virus (HCV), according to estimates (3). Many of these cases are asymptomatic or appear to have a mild disease course. The diagnosis of hepatitis C is often made after routine measurement of liver enzymes reveals elevated levels. However, HCV infection may progress to decompensated cirrhosis and hepatocellular carcinoma in a significant proportion of patients. Chronic hepatitis C is currently the leading indication for liver transplantation in the United States.

HCV infection accounts for most cases of non-A, non-B hepatitis (as described before 1992). Known risk factors for HCV infection include blood transfusions before 1992 (before initiation of routine HCV antibody screening of the blood supply), injecting drug use, needle-stick injuries, long-term hemodialysis, and a history of multiple sexual partners. Of these risk factors, injecting drug use carries the highest risk. A study of middle-class drug abusers in Rhode Island (4) determined that 76.7% of all patients who admitted to injecting drug use tested positive for HCV--an odds ratio of 22.6.

Of persons exposed to HCV, 85% experience chronic infection. A positive HCV antibody test using a second-generation enzyme-linked immunosorbent assay (ELISA) in a person with risk factors for HCV usually suggests ongoing infection, although a confirmatory test is always recommended. In patients who deny the risk factors stated previously, the relatively inexpensive recombinant immunoblot assay (RIBA) might be a useful

confirmatory test, since almost all persons with chronic infection have RIBA test results positive for HCV. However, in persons with one or more risk factors for HCV, a qualitative polymerase chain reaction test for detection of HCV RNA in serum is the recommended confirmatory test.

It is our opinion that HCV quantitation and genotyping at this time are helpful only in patients being considered for antiviral therapy. These tests are expensive and have no inherent diagnostic or prognostic value other than in the context of making treatment decisions.

Hepatitis B

Hepatitis B virus (HBV) infection affects 350 million people worldwide. In highly endemic areas, such as Asia and Africa, up to 15% of the population are long-term HBV carriers. The main routes of transmission in these areas are perinatal transmission (exposure to infected vaginal tract secretions and blood during labor) and horizontal transmission in childhood. The likelihood of chronic infection among persons exposed to HBV is inversely related to age: up to 95% of those infected at an age less than 5 years have chronic HBV infection (5). The risk is especially great if a child's mother has active hepatitis B viral replication; moreover, the risk is directly proportional to her level of viremia. By comparison, the risk of chronic infection is less than 5% among adults exposed to this virus.

In primary care clinics, neonatally acquired hepatitis B is generally detected through screening tests in high-risk patients, whereas adult-onset hepatitis B is often not detected until clinical signs of chronic liver disease develop.

The United States is a low-endemic area for HBV infection, and only 0.1% of the population is affected. Universal vaccination of infants has dramatically reduced the incidence of HBV infection in North America and Europe. Nevertheless, 200,000 to 300,000 new infections occur each year in the United States. The main routes of transmission in low-endemic areas appear to be sexual transmission between high-risk adults, injecting drug use, and occupational exposure to infected blood.

Serologic markers for HBV infection include hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), antibody to hepatitis B core antigen (anti-HBc), hepatitis B e antigen (HBeAg), and antibody to HBeAg (anti-HBe). Although these tests are helpful, serum HBV DNA testing is important to completely evaluate a patient with chronic HBV infection. Table 3 summarizes commonly encountered test results and their interpretation.

Alcoholic liver disease

Excessive alcohol intake can lead to both acute and chronic liver injury. A mildly elevated level of serum aminotransferase with an AST-ALT ratio of 2:1 is highly suggestive of alcoholic liver injury. In one study (6), more than 90% of patients with an AST-ALT ratio of at least 2:1 had alcoholic liver disease, and more than 96% of patients with a ratio of at least 3:1 had alcoholic liver disease. Besides the AST-ALT ratio, an elevated GGT level is often useful in the diagnosis of alcoholic liver disease. However, the

liver response that regulates GGT levels in the body is extremely sensitive, and the level of GGT may become elevated with even moderate consumption of alcohol. The reported sensitivity of an elevated GGT level for the detection of alcohol ingestion is 52% to 94% (7).

Alcoholic liver disease ranges from fatty liver to alcoholic hepatitis to alcoholic cirrhosis. Patients with fatty liver and alcoholic hepatitis often experience remarkable reversal in liver histopathologic characteristics and clinical symptoms with alcohol cessation.

Simple steatosis and nonalcoholic steatohepatitis

Nonalcoholic fatty liver disease comprises a spectrum from steatosis to NASH. The term *simple steatosis* is used to describe fatty deposition in the liver without the necroinflammatory changes or fibrosis, or both, that are present in NASH. Although steatosis and NASH may be associated with elevated serum aminotransferase levels, the natural history in these two entities is thought to be different. Steatosis is generally considered a benign and nonprogressive condition, whereas NASH may be associated with progressive injury that leads to fibrosis and cirrhosis in some patients. The most common risk factors for NASH include obesity (body mass index, >30), type 2 diabetes mellitus, hypertriglyceridemia, use of a variety of medications or toxins, and jejunoileal bypass (8) (table 4).

A detailed alcohol history needs to be obtained before a diagnosis of NASH is considered, because NASH may be histologically indistinguishable from alcoholic liver disease. Serum levels of AST and ALT may aid the physician in differentiating NASH from alcoholic liver disease, because patients with NASH usually do not have a greatly increased AST-ALT ratio. Although imaging studies such as ultrasound or computed tomography may suggest fatty infiltration of the liver, a biopsy is necessary to definitively establish the diagnosis. A biopsy is also crucial because it is currently the only means of differentiating between simple steatosis and NASH.

NASH is now recognized as a cause of cryptogenic cirrhosis, because there are no serologic markers for NASH and the characteristic findings of hepatic fatty infiltration and necroinflammation may disappear in late stages of the disease. Several recent studies (9,10) have found an increased prevalence of diabetes and obesity among patients with cryptogenic cirrhosis compared with patients who have cirrhosis from known causes. This evidence suggests that NASH may be an important etiologic factor in cryptogenic cirrhosis.

Autoimmune hepatitis

Autoimmune hepatitis should be included in the differential diagnosis of any patient with chronically elevated liver test results, particularly because autoimmune hepatitis is amenable to therapy. Type 1 autoimmune hepatitis, the most common form, typically occurs in young to middle-aged women. The female-male ratio is 4:1. About 30% of patients present with acute symptoms and laboratory derangements, ranging from hyperbilirubinemia to striking elevations in levels of serum aminotransferase. Some patients with autoimmune hepatitis are asymptomatic and have

only modest elevation of serum liver enzyme levels. There may be an association between autoimmune hepatitis and other autoimmune diseases, such as thyroiditis and rheumatoid arthritis (7).

The diagnosis of autoimmune hepatitis is suggested by serum tests that are positive for antinuclear antibodies, anti-smooth muscle antibodies, or hypergammaglobulinemia (an elevated gamma-globulin fraction on serum protein electrophoresis). A liver biopsy showing periportal inflammation, interface hepatitis, increased bridging necrosis, and diffuse infiltration of predominantly plasma cells confirms the diagnosis.

Hemochromatosis

Hereditary hemochromatosis is an autosomal recessive condition that primarily affects persons of Northern European ancestry. The *HFE* gene mutation, identified in 1996, is one of the most common inherited mutations among whites, and the carrier rate in Northern Europeans is as high as 1 in 11. Hereditary hemochromatosis is characterized by excessive gastrointestinal absorption of iron from a normal diet and subsequent iron deposition in the liver, heart, pancreas, anterior pituitary, skin, and joints (table 5). Although women may experience all the manifestations of iron overload, the degree of iron loading is usually lower in women than in men because of physiologic blood loss from menstruation.

Elevated serum aminotransferase levels may prompt testing for hemochromatosis, but many patients, even those with marked iron overload, have normal liver enzyme levels. The diagnosis of hemochromatosis should be suspected in patients with elevated serum transferrin-iron saturation (>45%) or an elevated serum ferritin concentration (ferritin, >200 ng/mL in women, >300 ng/mL in men), or both. Liver biopsy findings include increased stainable iron in hepatocytes (rather than Kupffer cells) with the greatest density of iron in periportal rather than pericentral hepatocytes. A hepatic iron concentration greater than 4,000 micrograms/g of liver dry weight and a hepatic iron index (hepatic iron concentration divided by age in years) greater than 1.9 are useful to distinguish homozygotes from heterozygotes and to identify patients with alcoholic liver disease who have compensated liver disease (11). However, the hepatic iron concentration and hepatic iron index are not "gold standards" for the diagnosis of hereditary hemochromatosis. They may be low in homozygotes with mild or minimal phenotypic expression or high in patients with end-stage liver disease who do not have hereditary hemochromatosis.

With the identification of the *HFE* gene mutation, the diagnosis of hereditary hemochromatosis can now be confirmed without a liver biopsy. Two *HFE* gene mutations were originally described: a "major" mutation involving a cysteine-to-tyrosine substitution at position 282 (C282Y) and a "minor" mutation involving a histidine-to-aspartate substitution at position 63 (H63D). The majority of persons of Northern European descent who commonly fit the classic phenotype for hereditary hemochromatosis are homozygous for the C282Y mutation or compound heterozygous for the C282Y and H63D mutations (12). However, a liver biopsy remains important to determine the presence or absence of

cirrhosis, particularly in patients with a serum ferritin concentration greater than 1,000 ng/mL at initial presentation.

Liver diseases linked to cholestatic pattern of injury

The two most common cholestatic liver diseases in adults are primary biliary cirrhosis and primary sclerosing cholangitis. Cholestatic liver injury can also be seen in biliary obstruction, infiltrative and granulomatous diseases, and hepatotoxic reactions to drugs or toxins.

Primary biliary cirrhosis

Primary biliary cirrhosis usually affects women in middle age. There is an association with other autoimmune diseases, such as sicca syndrome, thyroid dysfunction, scleroderma, and rheumatic disorders (1). Lymphocytic inflammation and destruction centered on small and medium-sized bile ducts lead to cholestasis, loss of bile ducts, fibrosis, or cirrhosis.

The classic finding on serum liver tests is an elevation of alkaline phosphatase level to three to four times the normal range, accompanied by either normal or elevated serum aminotransferase levels. Hyperbilirubinemia is present in only 10% of patients at presentation. The diagnosis is confirmed by a positive test for antimitochondrial antibody along with compatible histologic findings. About 5% of patients with primary biliary cirrhosis do not have antimitochondrial antibody. It is essential to exclude biliary tract disease in these patients by cholangiography or ultrasound. Some patients may have serologic tests or histologic findings suggestive of autoimmune hepatitis in addition to primary biliary cirrhosis. Such patients have been classified as having autoimmune cholangitis, autoimmune cholangiopathy, or "overlap syndrome."

Primary sclerosing cholangitis

Primary sclerosing cholangitis is a chronic inflammatory disease of the intrahepatic and extrahepatic biliary ducts that predominantly affects men aged 30 to 40 years. The male-female ratio is 2:1. Primary sclerosing cholangitis is strongly associated with ulcerative colitis. About 70% to 90% of patients with primary sclerosing cholangitis have inflammatory bowel disease (particularly ulcerative colitis), and 5% to 10% of patients with ulcerative colitis have primary sclerosing cholangitis (13). In this disease, chronic inflammation of the bile ducts leads to biliary strictures and increased risk of cholangitis, cirrhosis, and bile duct cancer (cholangiocarcinoma).

The classic serum biochemical profile for primary sclerosing cholangitis includes a twofold to threefold increase in alkaline phosphatase level coupled with a mild to moderate increase in serum aminotransferase (two to five times greater than normal). Perinuclear antineutrophil cytoplasmic antibody has been detected in up to 85% of patients with primary sclerosing cholangitis but is not specific to the disease. Cholangiography reveals multiple areas of intrahepatic and extrahepatic biliary stenoses with intervening dilatations. Fibro-obliterative bile duct lesions, the classic lesions found on liver biopsy, are present in only one third of cases. In fact, liver biopsy results are normal in 5% to 10% of cases because of the focal nature of the disease. Patients with

characteristic biopsy findings, a history of inflammatory bowel disease, and normal endoscopic retrograde cholangiopancreatography are labeled as having small-duct primary sclerosing cholangitis. This entity may account for up to 16% of cases of primary sclerosing cholangitis (14).

The role of liver biopsy

Most patients with abnormal liver test results have suspected etiologic factors for liver disease, identified by history taking, physical examination, further blood tests, and imaging (15). In patients with unexplained aminotransferase elevations, a liver biopsy is often helpful to identify the cause of liver disease. More importantly, a liver biopsy is invaluable in the staging of liver disease, which may also be helpful as an aid in prognosis and in assessing the risks and benefits of a possible therapy (16,17).

The decision to perform a liver biopsy must balance the possible risks of the procedure (eg, discomfort, bleeding, peritonitis, pneumothorax) with the potential benefits. Serious complications are rare (0.06% to 0.32%) (18). We advocate a liver biopsy for most patients with chronic liver disease because it is currently the only reliable way to identify the stage and grade of the disease. Knowing the stage and grade can provide prognostic information (eg, the presence or absence of cirrhosis), determine whether treatment is appropriate (eg, interferon and ribavirin combination therapy for chronic hepatitis C), or change management (eg, screening for hepatocellular carcinoma in patients with cirrhosis).

Conclusion

The primary care physician is often the first healthcare professional to identify patients who have abnormal liver test results. Persistently abnormal liver test results warrant further investigation that should include comprehensive history taking and physical examination, further blood tests, and imaging studies to arrive at a suspected diagnosis. A liver biopsy is of great value in establishing a final diagnosis and determining the stage and grade of disease. In many cases, referral to a specialist is important in helping to manage liver disease.

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