

New Development in Treating Liver Disorders: Approaches to liver function test from mild to fulminant disorders

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Abstract

When diagnosing patients with liver disorders, it is important to employ appropriate history taking and physical examination to narrow down the differential diagnoses that are suggested by patterns of abnormal liver functions (characterized by liver cell damage, cholestasis, or a combination of both) and to accurately determine the causative diseases on the basis of blood and imaging tests findings. Obtaining family history and past history concerning the chances of infection are important to differentiate viral diseases from non-viral ones. Although patients with mild impairment of liver function are often asymptomatic, it should be borne in mind that abnormal liver function tests are not unusual in patients with non-hepatic diseases such as thyroid disease. A patient with jaundice should first be examined for obstructive jaundice by abdominal ultrasonography or other diagnostic techniques. On the other hand, it is also important to evaluate the severity of liver disease in terms of hepatic reserve. In particular, in cases of acute hepatitis, it is necessary to evaluate hepatic reserve quickly and serially from early on to determine the rate of progress to reach severe or fulminant state. In addition, evaluation of hepatic reserve in liver cirrhosis is important not only for prognostication but also for selecting candidates for liver transplant and choosing the appropriate treatment of hepatocellular carcinoma associated with liver cirrhosis.

Key words Liver function test, Liver disorders, Fulminant hepatitis, Hepatic reserve

Introduction

As is clear from the fact that the liver has been called “a silent organ,” a diseased liver shows relatively few clinical signs unless the disease is severe or advanced. However, simple liver function tests using blood samples are widely available as part of routine health examination, providing opportunities for physicians to find abnormalities in liver function test results in daily clinical practice. On the other hand, because liver function abnormalities can be seen in patients who have no liver disease, correct diagnosis is

essential; when it is a liver disease, determination of its severity is also crucial. This paper discusses the critical points in the interpretation of liver function test results and approaches to the diagnosis of liver diseases, as well as prediction of progression of acute hepatitis to fulminant state and the hepatic reserve evaluation in patients with liver cirrhosis.

Process of Diagnosing Impaired Liver Functions

When diagnosing patients with liver disorders,

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Table 1 Key points of history taking in patients with impaired liver function

| |
|---|
| History of present illness |
| • Systemic symptoms (e.g., chills, fever, malaise) |
| • Gastrointestinal symptoms (e.g., anorexia, nausea/vomiting, abdominal pain, diarrhea) |
| • Skin symptoms (e.g., jaundice, itching, eruptions) |
| • Dark urine, alcoholic stools, etc. |
| Family history |
| • Presence/absence of patient(s) with liver disease |
| Past history |
| • Drinking history |
| • History of drug-use (including prescriptions, OTC drugs, health food products, and supplements) |
| • Surgery, blood transfusion, use of blood products |
| • Acupuncture, tattoo, needlestick accident, needle sharing |
| • Ingestion of raw foods (e.g., oysters, “sashimi” [sliced raw fish], raw meat/poultry) |
| • Record of overseas travel, sexual behaviors |

Table 2 Liver function tests and their significance

| | Diagnosis of liver cell damage | Diagnosis of cholestasis | Determination of severity |
|-------------------|--------------------------------|--------------------------|---------------------------|
| AST | ● | ● | |
| ALT | ● | ● | |
| ALP | ● | ● | |
| γ-GTP | ● | ● | |
| Total bilirubin | ● | ● | ● |
| Direct bilirubin | ○ | ● | ● |
| Total protein | ○ | | ○ |
| Serum albumin | ○ | | ● |
| ChE | ○ | | ● |
| Total cholesterol | ○ | ● | ● |
| Prothrombin time | ○ | ○ | ● |

●: Indispensable, ○: Should be included as far as possible.

[Adapted from Liver Function Study Team of the Affiliate Research Group of the Japanese Society of Gastroenterology (2007), pages 19–29.¹]

it is important to employ appropriate history taking and physical examination to narrow down the differential diagnoses that are suggested by patterns of abnormal liver functions (characterized by liver cell damage, cholestasis, or a combination of both), and to accurately determine the causative diseases on the basis of blood and imaging tests findings. **Table 1** shows the key points of history taking in patients with impaired liver function. Obtaining family history and past

history concerning the chances of infection are important to differentiate viral diseases from non-viral ones. In patients with jaundice, the urine coloration is useful for presuming the time of its onset. Although patients with mild abnormality of liver function are often asymptomatic, it should be borne in mind that abnormal liver function tests are not unusual in patients with non-hepatic diseases such as thyroid disease.

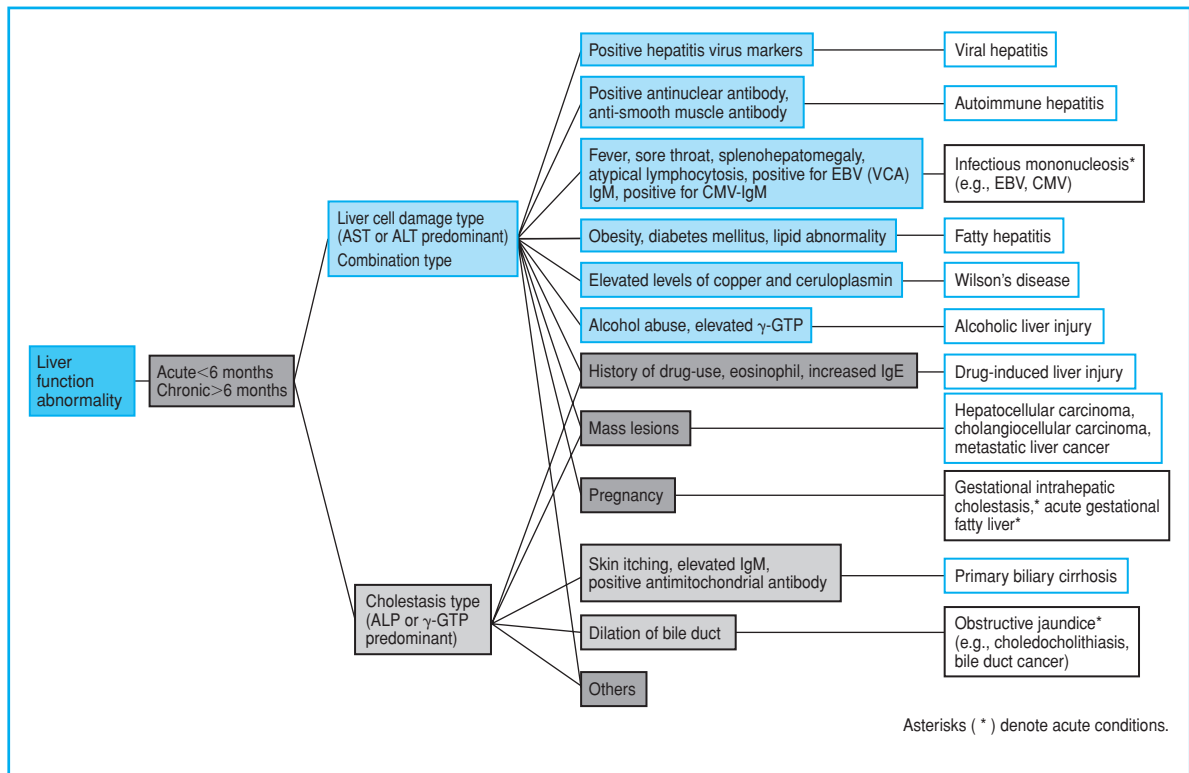


Fig. 1 Differentiation among liver function abnormalities

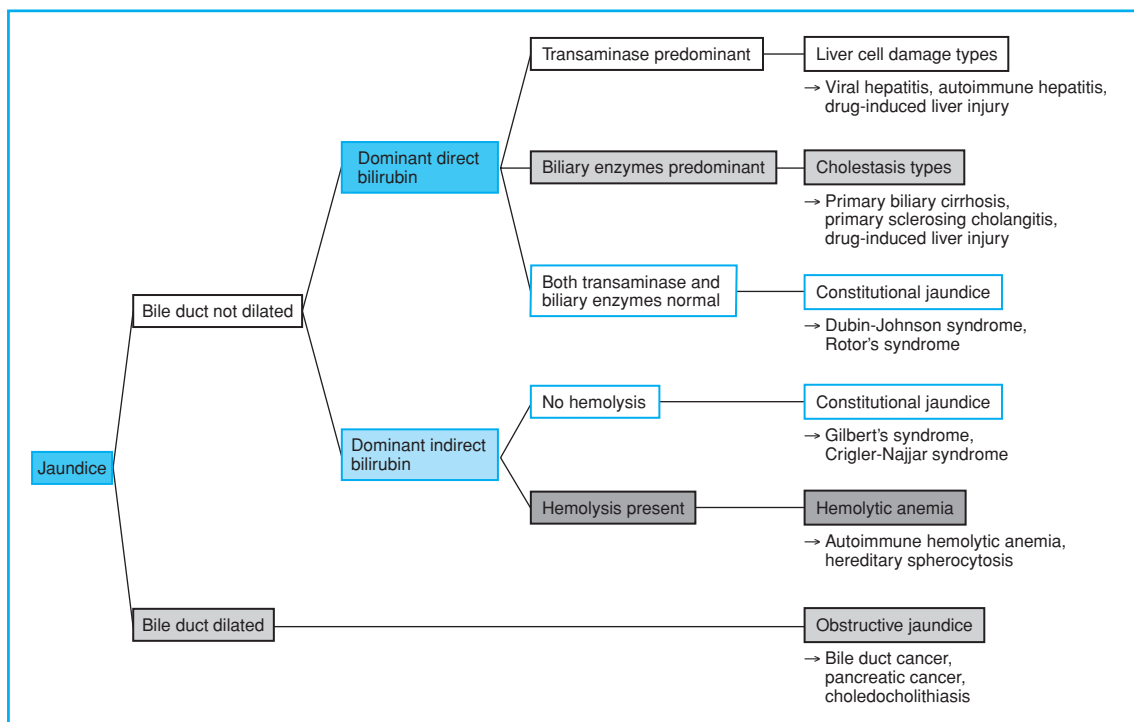


Fig. 2 Differentiation among conditions causing jaundice

Approaches to Interpret Liver Function Test Results

Table 2 presents the common items in liver function tests and their meanings.¹ When liver function abnormality is found, differentiation among the following three types helps to narrow down the causative disease: 1) the liver cell damage type, in which increases in transaminases [aspartate aminotransferase (AST) or glutamic oxaloacetic transaminase (GOT), alanine aminotransferase (ALT), or glutamic pyruvic transaminase (GPT)] are dominant, 2) the cholestasis type, in which increases in biliary enzymes [alkaline phosphatase (ALP), γ -glutamyl transpeptidase (γ -GTP)] are dominant, and 3) the combination type, in which increases in both enzymes are present (**Fig. 1**). Additionally, based on the history and duration of liver function abnormality, acuteness (worsened in less than 6 months) and chronicity (lasting more than 6 months) should be determined. On the other hand, when jaundice (elevated bilirubin) is present, the patient should first be examined for obstructive jaundice by abdominal ultrasonography or other diagnostic techniques (**Fig. 2**).

Elevated transaminases (namely AST and ALT)

AST and ALT, which are enzymes released into the blood with degeneration or necrosis of hepatocytes, serve as the most sensitive indices of liver cell damage. AST is present in the liver, cardiac muscle, skeletal muscle, kidney, brain, pancreas, lung, leucocytes, and erythrocytes (in descending order of quantity),² and the AST level in the blood becomes abnormally high when it escapes from these organs due to damage. Therefore, when predominantly elevated AST is present, not only liver diseases (e.g., liver cirrhosis, liver cancer, alcoholic liver damage, early stage of acute hepatitis) but also other diseases such as myocardial infarction, thyroid disease, collagen disease, and muscular disease should be taken into consideration. Because the liver contains more ALT than other organs, it is more specific to liver damage. Predominant elevation of ALT is found in cases like hepatitis and fatty liver. ALT levels of 500 IU/l or higher reflect acute liver cell necrosis, whereas lower levels suggest mild cases of acute liver cell necrosis, convalescent stage of acute hepatitis, active stage of chronic hepatitis, liver cirrhosis, liver cancer, or biliary disorders

such as obstructive jaundice. Vigorous exercise or alcohol intake may temporarily increase the ALT level by less than 100 IU/l.³

Elevated biliary enzymes (namely ALP and γ -GTP)

ALP and γ -GTP, called biliary enzymes, are enzymes that have a propensity to be localized in the bile canalicular membrane of the hepatocyte. ALP is an enzyme that hydrolyzes phosphoric monoesters under alkaline conditions and is distributed over almost all organs, especially in the bone, epithelium of the small intestinal mucosa, liver, and placenta. γ -GTP is an enzyme that catalyses the hydrolysis of glutathione and transfer of the γ -glutamyl group from one peptide to another or to an amino acid, and it is specific to liver diseases. In cases of liver and biliary diseases it is common that both ALP and γ -GTP levels increase; marked increases are found particularly in cases of intrahepatic cholestasis and obstructive jaundice. The levels of biliary enzymes also rise in localized diseases such as liver cancer and liver abscess, and mild elevation of these enzymes are also found in diffuse liver diseases (e.g., hepatitis, liver cirrhosis). Elevated levels of biliary enzymes may also be found in other diseases such as pancreatic disease, myocardial damage, lung disease, and diabetes mellitus.

When ALP alone is elevated, isozyme analysis (ALP1 through 6) should be conducted. If elevated ALP1 (high-molecular-weight ALP) and ALP2 (hepatic ALP) are dominant, liver and biliary diseases should be suspected. If ALP3 (osseous ALP) is elevated, it may be due to osteogenetic disease or thyroid disease. On the other hand, in patients with liver cirrhosis or high-fat diet (in patients with the blood type of B or O), ALP5 (small-intestinal ALP) is elevated. An increase in γ -GTP alone may occur in association with alcohol intake or the use of anticonvulsant drugs, which is a result of enzyme induction.

Elevated serum bilirubin

The source of 70 to 90% of bilirubin is decomposed hemoglobin of senescent erythrocytes. Hemoglobin is decomposed into globin and heme in the reticuloendothelial system, and the heme molecule loses its iron and ring-shaped structure to form bilirubin. The produced indirect (unconjugated) bilirubin undergoes glucuronide conjugation in the liver, and the formed

Table 3 Child-Pugh classification

| | 1 point | 2 points | 3 points |
|--------------------------|---------|----------|-----------------|
| Encephalopathy | None | Mild | Occasional coma |
| Ascites | None | Slight | Moderate |
| Serum bilirubin (mg/dl) | <2.0 | 2.0–3.0 | >3.0 |
| Serum albumin (g/dl) | >3.5 | 2.8–3.5 | <2.8 |
| Prothrombin activity (%) | >70 | 40–70 | <40 |

The severity of liver disease is classified into the following three grades in terms of the total score obtained by adding the points from each item: Grade A, 5–8 points; Grade B, 7–9 points; and Grade C, 10–15 points.

[Extracted from Liver Cancer Study Group of Japan (2008), pages 15–16.^{5]}

direct (conjugated) bilirubin is secreted from the liver into the bile.

If the blood level of water-soluble direct bilirubin exceeds 1.5 mg/dl, bilirubinuria (dark urine) occurs, and the bulbar conjunctive becomes yellow when a total bilirubin level is 3.0 mg/dl or more. When jaundice is noted, it is important to first examine the presence of obstructive jaundice by abdominal ultrasonography or other diagnostic techniques (**Fig. 2**). If obstructive jaundice is excluded, the dominance of direct or indirect bilirubin should be determined. Although direct bilirubin is predominant in cases of liver cell damage, the proportion of indirect bilirubin gradually increases as liver failure progresses in cases of liver cirrhosis or fulminant hepatic failure (meaning the ratio of direct bilirubin to total bilirubin decreases). If indirect bilirubin is predominant, differentiation between constitutional jaundice and hemolytic anemia is necessary, for which the presence/absence of hemolysis is the key.

Evaluation of severity (hepatic reserve)

When liver and biliary disease is responsible for impaired liver function, the severity of the disease and the remaining liver function (hepatic reserve) should be evaluated on the basis of total bilirubin, direct bilirubin, serum albumin, cholinesterase (ChE), total cholesterol, and prothrombin time (**Table 2**). Serum albumin, ChE, total cholesterol, and prothrombin time are important indices of protein synthesis, which will decrease in cases of liver cirrhosis and fulminant hepatitis.

In cases of acute hepatitis, early detection of progression to fulminant hepatic failure is necessary, and thus serial evaluation of hepatic reserve over time is critical. In Japan, fulminant hepatic

failure is defined as a hepatitis that causes hepatic coma of grade II or higher within 8 weeks after the onset of the initial symptoms due to severe hepatic dysfunction accompanied by a prothrombin time of 40% or less. In severe acute hepatitis with no impaired consciousness but with a prothrombin time of 40% or less, about 30% of the cases develop into fulminant hepatic failure. Prothrombin time reflects the activity of clotting factors produced in hepatocyte (factors I, II, V, VII, IX, and X). Since the half-lives of these clotting factors are as short as several hours to several days, the examination of prothrombin time is extremely helpful in the evaluation of hepatic reserve, even when the disease is progressing rapidly.

When there are marked gastrointestinal symptoms such as anorexia and vomiting as well as prominent general malaise, and when high levels of serum bilirubin persist and the [direct bilirubin/total bilirubin ratio] ratio drops even after AST and ALT decline, there is a risk of progression to fulminant hepatic failure. The examination of serum hepatocyte growth factor (HGF) level is considered useful in predicting development and prognosis of fulminant hepatic failure, since serum HGF increases gradually along with the pathologic process reaching 1 ng/ml or greater in fulminant hepatic failure.⁴

On the other hand, although the platelet count decreases as chronic liver disease progresses to liver cirrhosis, thrombopenia in cirrhosis has been attributed to hypersplenism and impaired production of the platelet hematopoietic factor, thrombopoietin. Considering that liver cirrhosis can often accompany hepatocellular carcinoma, evaluation of the severity (hepatic reserve) of

liver cirrhosis is very important not only for its prognostification but also to prepare for hepatocellular carcinoma to allow proper treatment selection and to make a prognosis. In general, the Child-Pugh classification (**Table 3**) is used to evaluate hepatic reserve, in which scores that reflect the levels of encephalopathy, ascites, total bilirubin, serum albumin, and prothrombin time are added and classified into three grades (A, B and C).⁵

Conclusion

“Reading liver function test results” is to understand the meanings of a wide variety of test items, to enumerate differential diagnoses based on patterns of abnormal test data, and to determine the most probable diagnosis based on the patient’s clinical history and physical findings—as though one is to comprehend the depth of a detective novel. Even in busy daily clinical practice, we believe following such thinking process provides efficient approaches to prompt and accurate diagnosis and opportunities to cultivate ability in reading liver function test results.

References

1. Liver Function Study Team of the Affiliate Research Group of the Japanese Society of Gastroenterology, ed. *Criteria for Choosing Hepatitis Virus Markers and Liver Function Tests*. Tokyo: Bunkodo Co., Ltd.; 2007:19–29. (in Japanese)
2. Pratt DS, Kaplan MM. Evaluation of liver function. In: Fukui T, Kurokawa K, eds. *Harrison’s Principles of Internal Medicine. The Japanese 2nd ed.* Tokyo: Medical Sciences International, Ltd.; 2006:1867–1870. (in Japanese)
3. Kawai T, Yakata M, Itoh Y, eds. *Mechanisms of Abnormal Test Results*. 5th ed. Tokyo: Igaku-Shoin Ltd.; 2008:241–274. (in Japanese)
4. Tsubouchi H, Kawakami S, Hirono S, et al. Prediction of outcome in fulminant hepatic failure by serum human hepatocyte growth factor. *Lancet*. 1992; 340–307.
5. Liver Cancer Study Group of Japan, ed. *The General Rules for the Clinical and Pathological Study of Primary Liver Cancer*. 5th ed. Tokyo: Kanehara & Co., Ltd.; 2008:15–16. (in Japanese)