Abnormal Liver Blood Tests: Primary Care Approach

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Abstract

Background: According to recent epidemiological data, annual deaths due to liver disease have increased dramatically, while predictions show that trends will continue to rise in the upcoming years. **Summary:** Abnormal liver blood tests are one of the most common challenges encountered in the primary care setting. The prevalence of mildly elevated transaminase levels is around 10–20% in the general population. The most common causes for the rising burden of liver disease are nonalcoholic fatty liver disease (NAFLD), alcohol-related liver disease (ARLD), and viral hepatitis. With improvements in the management of viral hepatitis over the last decades, the causes for the rising burden of liver disease are shifting toward ARLD and NAFLD. It is well-known that liver disease usually progresses silently for years or decades until the complications of cirrhosis occur. The majority of patients will not require referral to a specialist but will need further assessment in primary care. They should be evaluated for the etiology of liver disease irrespective of the duration of abnormal liver blood tests or unmarked clinical presentation. The evaluation should include a history of alcohol use, a history of medicines or herbal supplements, testing for viral hepatitis, and assessment for NAFLD, especially in obese

patients and patients with type 2 diabetes. Abdominal ultrasound should be performed. **Key Messages:** The general practitioner may contribute significantly by identifying and screening patients at risk for chronic liver disease, as well as prioritize individuals with symptoms or signs of advanced liver disease to the specialist clinic.

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Introduction

Annual deaths due to chronic liver disease (CLD) have increased dramatically in the last decade all over the world. According to recent epidemiological data, CLD is the fourth leading cause of death among people aged 45–64 years in the USA [1]. Moreover, hospitalizations due to CLD have doubled over the last decade, while predictions show that trends will continue to rise in the upcoming years [2]. Recent data from the UK stresses the continuing increase in the burden of liver disease from excess alcohol consumption and obesity in the population younger than 65 years [3]. The 3 most common causes for the rising burden of liver disease and primary liver cancer are nonalcoholic fatty liver disease (NAFLD), alcohol-related liver disease (ARLD), and viral hepatitis B and C [4–6].

In everyday practice, patients with abnormal liver blood tests and clinical signs and symptoms suggestive

for liver disease should be sent to a hepatologist for further evaluation. However, approximately 50% of patients with advanced liver disease referred for the first time to a hepatologist have been previously noted to have abnormal liver blood tests in medical records but with incomplete investigation and follow-up [7]. Moreover, it is estimated that the prevalence of mildly elevated transaminase levels is between 10 and 20% in the general population [8]. Furthermore, it is important to stress that liver enzymes may fluctuate, irrespective of the stage of liver disease, although normal liver biochemistry does not rule out liver disease [9, 10]. On the other hand, it is well known that CLD usually progresses silently for years or even decades until the complications of hepatic insufficiency or portal hypertension occur [9]. Thus, it is important to carefully examine the etiology of potential liver disease in primary care settings, irrespective of the duration of abnormal liver blood tests or unmarked clinical presentation (even if a patient is symptom-free and without signs of liver disease) [11, 12]. This clinical scenario of abnormal liver biochemistry in an otherwise healthy-looking individual has been often a challenge even for the experienced physician [13].

Common Etiologies for Abnormal Liver Blood Tests

The most common causes of abnormal liver blood tests are NAFLD, ARLD, viral hepatitis, drug-induced liver injury, and hemochromatosis [2, 4, 5]. Less common causes include autoimmune hepatitis, primary sclerosing cholangitis (PSC), and primary biliary cholangitis, while Wilson's disease and alpha-1 antitrypsin deficiency are rare causes of inherited chronic liver disorders [6, 9].

Extrahepatic disorders that can cause asymptomatic transaminase elevation are celiac disease, thyroid gland diseases, hemolytic anemia, inflammatory bowel disease, and muscle disorders such as polymyositis and rhabdomyolysis. Moreover, transaminases can be elevated after strenuous exercise in an otherwise healthy individual [14].

Differences Based on Laboratory Tests

Liver chemistry tests have been referred to in everyday clinical practice, such as liver functional tests (LFTs), and typically include serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), serum bilirubin (total and conjugated bilirubin), and measure-

ment of synthetic liver function tests, prothrombin time (PT), and serum albumin level [9, 10].

Tests of Hepatocellular Injury

In everyday clinical practice, an LFT panel is usually interpreted as a hepatocellular or cholestatic liver injury based on the pattern of elevation. Elevated serum transaminases are typically seen in a hepatocellular injury, while a disproportionate elevation of ALP and GGT, in comparison to transaminases, mostly represents an obstruction of the biliary system. Although specific liver diseases may display a mixed biochemical pattern (elevation of AST and ALT levels together with elevation of ALP and GGT levels), differential diagnosis is of crucial importance to distinguish between the 2 subgroups of abnormal LFTs [10].

In addition to the magnitude of transaminase elevations, the De Ritis ratio (ratio of AST to ALT) can be useful in determining the etiology of elevated transaminases. Typically, patients with alcoholic liver disease have an AST/ALT ratio >2 . On the other hand, for most liver conditions including chronic viral hepatitis and NAFLD, ALT levels are greater than AST levels. Conversely, in chronic viral hepatitis, chronic alcoholism, or NAFLD, an elevated AST/ALT ratio is predictive of long-term complications including fibrosis and cirrhosis. Thus, AST $>$ ALT can be seen in patients with cirrhosis of any etiology, although AST/ALT is typically not $>2:1$ [11, 12].

An abnormal LFT level is usually defined as a value exceeding the upper reference limit, but physicians should be aware of different reference limits among laboratories, as well as different aminotransferase levels based on age and sex. While ALT is more specific to liver damage, AST may be released from different organs such as the skeletal muscles, heart, kidney, and brain [13].

Tests of Cholestatic Liver Injury

ALP is present in the epithelial cells of bile ducts, and its elevation is typically seen in cholestatic liver disease. Cholestatic liver disease can be categorized as either mechanical obstruction to bile flow (extrahepatic cholestasis) or impairments of bile formation by the hepatocytes (intrahepatic cholestasis). Biliary dilatation suggests an extrahepatic cause, while a normal biliary system on abdominal ultrasound suggests that the cause of elevated ALP is intrahepatic. Extrahepatic causes of cholestasis in-

clude choledocholithiasis and obstruction of the biliary tract due to malignancy. However, the enzyme ALP is expressed on the surface of osteoblasts; thus, isolated elevation of ALP can be seen in bone disease, bone metastasis, and vitamin D deficiency. During pregnancy, ALP is released from the placenta, although its levels are known to gradually increase from the late first trimester to the term of delivery. ALP can also be released from other organs, such as the intestines and kidney [10].

GGT is predominantly used as a laboratory marker for liver disease, although it is present in the cell membranes of many tissues. However, serum elevation of GGT is usually seen together with elevated ALP in cholestatic liver disease. The 2 laboratory markers ALP and GGT correlate well and can be used for distinction between liver and bone diseases. Isolated elevation of the serum GGT level may be due to recent excessive alcohol consumption, NAFLD, obesity, and drug-induced liver injury [12, 14]. Recent evidence suggests that GGT may be a strong predictive biomarker of cellular antioxidant inadequacy and risk of metabolic syndrome, diabetes, cardiovascular disease, and all-cause mortality [15–17].

Serum bilirubin may be elevated in both hepatocellular and cholestatic patterns but also in different extrahepatic disorders. In the case of hyperbilirubinemia, the first step is to fractionate the bilirubin into conjugated and unconjugated components. Conjugated hyperbilirubinemia is usually present in parenchymal liver disease (hepatocellular disease) and cholestatic liver disease (intrahepatic and extrahepatic).

Unconjugated hyperbilirubinemia is usually present due to hemolysis or Gilbert's syndrome, but the physician should consider even rare causes of isolated unconjugated hyperbilirubinemia such as Crigler-Najjar syndrome [14, 18, 19]. However, the most common cause of isolated unconjugated hyperbilirubinemia with other normal liver enzymes is Gilbert's syndrome, a genetic disorder that affects between 4% and 16% in different populations [20]. If the patients have predominant unconjugated hyperbilirubinemia with concomitant anemia, hemolysis needs to be excluded by requesting reticulocyte count, serum lactate dehydrogenase (LDH) and haptoglobin. Table 1 summarizes the causes of different liver blood test elevation.

Synthetic Liver Function Tests

PT or the international normalized ratio (INR) and serum albumin can be associated with a decrease in synthetic liver function, although neither is specific for liver

disease. PT is used to evaluate the extrinsic and common pathways of coagulation, which would detect deficiencies of clotting factors (II, V, VII, and X), and low fibrinogen concentrations that are produced in the liver. Thus, prolonged PT/INR due to compromised production of clotting factors is typically seen in significant loss of synthetic liver function and liver insufficiency. Prolonged PT/INR may be due to acute or chronic liver insufficiency, but it can also be caused by fat malabsorption and consequent vitamin K deficiency in cholestatic liver disease, or extrahepatic disorders, including malabsorption, dysbiosis, and hematologic disorders [9, 14].

Albumin is a protein that is produced in the liver. Serum albumin level is often used as a marker of synthetic liver function. However, it should be interpreted with caution as albumin can be a marker of inflammation and has implications in acute and/or chronic inflammatory diseases. Low serum albumin is typically found in acute infection, sepsis, and chronic inflammatory disorders but also in many other conditions such as heart failure, malnutrition, malabsorption, chronic renal failure, nephrotic syndrome, and protein losing enteropathy [10, 12].

Other Laboratory Abnormalities in CLD

Low platelet count (thrombocytopenia) is one of the most common hematological abnormalities found in CLD. Thrombocytopenia may be one of the early laboratory markers of advanced liver disease and portal hypertension. The mechanism is multifactorial, including decreased production due to bone marrow suppression (caused by toxins including alcohol, drugs, and iron overload), splenic sequestration, and increased splenic destruction (as a consequence of portal hypertension) [9, 14].

LDH is not specific to the liver, as this enzyme is present in large amount in the liver, heart, and muscles and insult to any of these organs can result in elevation of serum LDH. Although LDH is not a reliable liver test, it is typically elevated in liver diseases associated with hemolysis, solid tumors, lymphomas, and viral hepatitis, or during ischemic injury.

The Initial Approach in Primary Care Settings

The initial approach to a patient with abnormal liver blood tests consists of careful evaluation for potential causes of liver disease, including past medical history and physical examination. The history of alcohol use should

Table 1. Most common conditions associated with abnormal liver blood tests

Liver blood test	Liver disease	Extrahepatic disease and conditions
Aminotransferases (AST and ALT)	Hepatocellular injury (any acute liver disease or CLD): ARLD, NAFLD, AIH, viral hepatitis, biliary obstruction, genetic liver diseases (hemochromatosis and Wilson's disease), DILI, toxic hepatitis, and ischemic hepatitis	Celiac disease, heart failure, skeletal muscle disease, hyperthyroidism, kidney, brain, parenteral nutrition, and malnutrition; Any liver disease in pregnancy (HELLP and fatty liver disease) and strenuous exercises
ALP	Cholestasis (extrahepatic and intrahepatic), cholestatic liver diseases (PBC and PSC), DILI, cirrhosis, primary liver tumors, metastatic liver disease, and intrahepatic cholestasis in pregnancy	Pregnancy (placenta origin); intestine (gastric ulcer), bone disease and bone metastasis, children during growth, sarcoidosis, tuberculosis, amyloidosis, hyperthyroidism, hyperparathyroidism, and lymphoma
GGT	Cholestasis (extrahepatic and intrahepatic), cholestatic liver diseases (PSC and PBC), ARLD, NAFLD, medications, infiltrating liver disease, primary liver tumors, and metastatic liver disease	DILI, hyperthyroidism, hyperparathyroidism, sepsis, and lymphoma
Bilirubin	Any acute liver disease and CLD and cirrhosis, genetic disorders of abnormal bilirubin metabolism, cholestatic hepatitis, ischemic hepatitis, medications, and intrahepatic cholestasis in pregnancy	Hemolysis, hemolytic anemia, heart failure, parenteral nutrition, sepsis, lymphoma, sarcoidosis, and amyloidosis

ARLD, alcohol-related liver disease; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; DILI, drug-induced liver injury; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CLD, chronic liver disease.

elicit the average amount of alcohol consumed each day, the pattern of drinking, and the impact of drinking on the patient's well-being.

The medication history should be assessed for potential hepatotoxins, including prescribed or nonprescribed medications, dietary supplements, herbal remedies, and occupational exposure to chemicals. Drug-induced hepatotoxicity is a frequent cause of liver injury. Almost any medication can have a toxic effect on the liver, altering liver enzyme levels. Drug hepatotoxicity can be predictable (as in the case of acetaminophen) or unpredictable (idiosyncratic), which is low frequency. Drug-induced liver disease mimics all forms of hepatobiliary diseases, including acute and chronic hepatitis, and acute cholestasis, or can be presented with a mixed pattern [9, 10].

Individuals with features of metabolic syndrome, including obesity, type 2 diabetes (T2DM), hypertension, and dyslipidemia, are at highest risk for NAFLD. Any of these components increases the risk for NAFLD [4, 5].

Patients at high risk for viral hepatitis are individuals with a history of injecting drugs (PWID), men who have sex with

men, migrants from high-prevalence areas, and prisoners. Other risk factors include tattooing, piercing, and blood transfusions prior to 1992. Vertical transmission from mother to child still has a major impact on disease burden regarding B hepatitis in some parts of the world [6, 21, 22]. In patients with acute onset of jaundice, right-quadrant abdominal pain, light-colored stool, and dark urine, a history of gallstones and choledocholithiasis is recommended.

Less common medical conditions associated with CLD are heart failure, celiac sprue, thyroid gland diseases, muscle disorders, and alpha-1 antitrypsin deficiency (early emphysema in childhood). Individuals with autoimmune diseases are at a higher risk for autoimmune liver disease. Autoimmune liver disease tends to develop silently with nonspecific symptoms and with no signs until the end-stage liver disease develops. Most of these patients will present with nonspecific symptoms including fatigue and malaise; thus, liver blood tests may be appropriate in these patients.

Patients with inflammatory bowel disease (IBD) have a higher risk of developing autoimmune cholestatic liver disease. Up to 30% of IBD patients have altered liver blood tests.

PSC may affect up to 5% of IBD patients, while 70–80% of patients with PSC have concomitant IBD [20, 23, 24].

Liver diseases that are unique to pregnancy are hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy, and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets). The initial evaluation of a pregnant woman with abnormal LFTs includes the same standard workup as that of nonpregnant patients. However, liver blood chemistry may be abnormal but not necessarily of clinical concern in pregnancy, as serum ALP is often elevated and serum albumin can be frequently reduced [25].

Physical Examination

Physical examination should assess signs of liver disease. Liver disease can appear to be symptom-free for a long period of time or may be associated with nonspecific symptoms including abdominal pain, weight loss, pruritus, malaise, and fatigue. Thus, physical examination in patients with abnormal liver blood tests is typically normal.

On the other hand, patients with advanced CLD may have upon physical examination, typical signs of liver insufficiency and/or portal hypertension. Signs of liver insufficiency and portal hypertension are jaundice, spider nevi, ascites, leg edema, palmar erythema, gynecomastia, caput medusae, fetor hepaticus, coagulopathy skin hematoma, Dupuytren's contracture, parotid gland enlargement, testicular atrophy, muscle atrophy, enlarged spleen, signs of hepatic encephalopathy, and sleep-wake abnormalities [26, 27]. The presence of a palpable liver might be due to hepatomegaly, while a firm liver edge is typically due to cirrhosis. The presence of signs or symptoms of advanced CLD or acute liver failure should lead to an immediate referral to a specialist clinic for hospitalization.

Laboratory and Imaging Tests in Primary Care Settings

Patients with abnormal liver chemistry tests should be considered for further laboratory and imaging tests irrespective of the duration of abnormality. A standard liver blood test should include evaluation of complete blood count, AST, ALT, ALP, GGT, bilirubin (total and conjugated bilirubin), serum albumin, iron, transferrin saturation, and ferritin. In patients highly suspected of NAFLD (obesity and T2DM), fasting glucose, fasting lipid level, HOMA index, or hemoglobin A1c test (HbA1c) should be evaluated.

Raised ferritin levels can be commonly seen in different CLDs (like NAFLD and ARLD) but also in patients with acute or chronic inflammatory disease of different etiology. Moreover, it is estimated that the prevalence of elevated ferritin levels varies between 4% and 41% in healthy populations. A typical laboratory finding in hereditary hemochromatosis is transferrin saturation >45%, together with a high ferritin level [28, 29]. In primary care settings, the standard clinical approach for patients with suspicion of NAFLD should include abdominal ultrasound, as it will be discussed later in this article.

Patients with risk factors for viral hepatitis should be evaluated for hepatitis B surface antigen and hepatitis C antibody testing, and if positive, be referred to a specialist clinic in accordance with local guidance. Patients with marked elevations of transaminases (ALT >1,000 U/L) should immediately be referred to a specialist clinic [6, 30].

In primary care settings, the standard clinical approach for patients with elevated ALP of hepatic origin should include abdominal ultrasonography to assess the hepatic parenchyma and bile ducts. Biliary dilatation or any clinically relevant abnormalities on ultrasound require further imaging assessment (MRCP, ERCP, etc.) and consideration of urgent referral to hospital, depending on the findings and clinical settings. Approach to the patient with abnormal liver blood tests is shown in Figure 1.

Clinical Approach to Common Conditions in Primary Care Settings

As previously said, the most common causes of abnormal liver blood tests are NAFLD, ARLD, and viral hepatitis B and C. Majority of the patients with elevated liver enzymes due to NAFLD or ARLD will not necessarily require referral to a specialist but will need further assessment in primary care. For this reason, it is of at most importance for a physician to estimate if there is significant liver fibrosis in order to prevent progression to cirrhosis and end-stage liver disease. The main strategy for patients without high risk for progression and significant fibrosis is to encourage them for lifestyle changes.

Nonalcoholic Fatty Liver Disease

NAFLD is present in 17–46% of adults in Western countries and between 42 and 70% in individuals with (T2DM) [31]. All individuals with persistently abnormal liver enzymes should be screened for NAFLD, as

Fig. 1. Initial approach to abnormal liver chemistry. Patients with marked abnormalities of liver blood tests and/or suspicious clinical signs and symptoms should be considered for urgent referral to a specialist. FBC, full blood count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase;

GGT, gamma-glutamyltransferase; TB, total bilirubine; PT, prothrombin time; INR, international normalized ratio; LFTs, liver function tests; HbA1c, hemoglobin A1c; NAFLD, non-alcoholic fatty liver disease; HCV Ab, hepatitis C virus antibody; HBsAg, hepatitis B surface antigen.

NAFLD is the main reason for unexpectedly elevated liver enzymes [31]. Patients who have metabolic risk factors, including BMI >25, arterial hypertension, dyslipidemia, insulin resistance, or T2DM, should be further assessed for NAFLD. Patients with T2DM should be screened for the presence of NAFLD and fibrotic nonalcoholic steatohepatitis irrespective of liver enzyme levels, since T2DM individuals are at high risk of disease progression [31, 32]. Moreover, patients with nonalcoholic steatohepatitis and hypertension should have closer monitoring because of a higher risk of disease progression. However, abdominal ultrasound is sensitive for the detection of liver steatosis only when hepatocytes are more than 30% steatotic, while patients with milder steatosis might have normal ultrasound. On the other hand, approximately up to 25% individuals who had “fatty liver” had normal BMI. The reported prevalence of nonobese NAFLD varies widely, ranging from 3 to 30% [33, 34]. At primary settings, patients with NAFLD should be assessed for the stage of liver fibrosis. First-line testing should include either the fi-

brosis-4 (FIB-4) score or the NAFLD Fibrosis Score (NFS)[9, 35, 36]. Individuals with elevated FIB-4 or NFS should be considered for referral to a hepatologist.

The current standard of care approach for patients with NAFLD include lifestyle changes regarding physical activity and dietary changes in order to reduce visceral adiposity [32, 37]. Patients with NAFLD require reinforcement of lifestyle changes regarding dietary restriction and physical activity. Another important strategy is to follow up in order to prevent progression of disease, and to promote early referral to a specialist center for liver biopsy or further investigation if needed [33, 34, 37].

Alcohol-Related Liver Disease

Screening for regular alcohol consumption should be a priority in everyday clinical practice. A daily alcohol consumption of 30 g for men and 20 g for women indicates ARLD. There is without a doubt a relationship

between the amount of alcohol consumption and liver injury, but several cofactors may contribute including type of alcohol beverage, drinking patterns (daily drinking or binge drinking), duration of exposure, and genetic susceptibility. Patients with ARLD should be encouraged to cease alcohol consumption and be referred to a multidisciplinary team according to local guidance [38].

Viral Hepatitis

Chronic hepatitis B and hepatitis C still represent a major public health concern in Europe, despite the advent of novel therapeutic modalities [39]. Since most patients with chronic viral hepatitis are asymptomatic until the advance phase of CLD and cirrhosis, the initial diagnosis relies on primary care physicians to identify and screen high-risk groups of patients [40, 41]. Timely recognition and screening of patients at risk is crucial in order to prevent the progression of the disease. The role of GP in prevention of progression and transmission of disease is crucial. It is important to improve adherence to local guidelines for hepatitis B and hepatitis C testing within a single primary care clinic. Furthermore, a patient with elevated liver blood tests should be evaluated for antibody and hepatitis B surface antigen, irrespective of duration and level of abnormal liver blood tests, or unmarked clinical presentation [39, 42].

Conclusion

Abnormal liver blood tests are one of the most common challenges encountered in the primary care setting. Clinical approach in primary care clinics is very important and consists of medical history, physical examination, and extended laboratory and imaging testing in order to determine the diagnosis. The general practitioner may contribute significantly by identifying and screening patients at risk for CLD, as well as prioritizing those who present with symptoms and signs of advanced liver disease to the specialist clinic based on the local guidance.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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