

LIVER MYSTERIES

Rami Sleem MD, Tarun Kothari MD, FACP, FACP

The liver is the largest solid organ in the body, weighing about 1.5 kg in the adult. It lies in the right upper quadrant of the abdomen, overlying the gallbladder, and is completely protected by the thoracic rib cage. The liver and gall bladder are connected via ducts that ultimately pour bile in the small intestine. The liver is the only internal human organ capable of natural regeneration of lost tissue, with as little as 25% of a liver can regenerate into a whole liver.

The liver has a wide range of functions, ranging from detoxification of drugs and toxins our body is exposed to via various routes, carbohydrate/protein/fat metabolism, digestion through bile synthesis, storage of carbohydrates/vitamins/minerals, and last but not least production of coagulation factors and a couple of hormones. The liver is necessary for survival; there is currently no way to compensate for the absence of liver function.

Due to the multitude of functions, the liver is prone to many diseases. The most common disease is called NAFLD (non alcoholic fatty liver disease) which is fat deposits in the liver and is further divided into two subtypes, steatosis and steatohepatitis, with the latter being more severe. The second most common is Hepatitis C virus infection; (hepatitis means inflammation/infection of the liver). Other common causes of liver diseases include hepatitis A, B (with or without D), and E viruses, alcohol abuse, medications (including herbal), illicit drugs, and toxins. Less common diseases include Wilson's disease (excess copper), hemochromatosis (iron overload), duct disease (primary biliary cirrhosis and primary sclerosing cholangitis), autoimmune (body's own immune system attacks liver), and deficiency of an enzyme called alpha-1 anti-trypsin. These conditions can ultimately lead to liver cirrhosis and cancer.

Because of the close proximity of the gall bladder to the liver and the ducts connecting the two organs, diseases of the gall bladder can also result in liver injury. Gall bladder stones can pass through the bile ducts and get stuck, obstructing bile flow which can lead to inflammation and infection. Cancer of the ducts can also spread to the adjacent liver.

Classic symptoms of liver disease can include fatigue, yellowish discoloration of the skin (jaundice) and eyes (icterus), generalized itching, pale stools, dark urine, swelling in abdomen/ankles/feet, and easy bruising/nose bleeds. Other non-specific accompanying symptoms can include painful joints/muscles, abdominal pain, loss of appetite, and weight loss.

The first tests doctors order to screen for liver disease are a set of liver enzymes that are present in liver and duct cells. These are the aminotransferases (ALT and AST), alkaline phosphatase (AP), and gamma glutamyl transpeptidase (GGT). Other tests for liver disease include serum albumin (a protein synthesized by the liver), INR (a measure of clotting factors in the body which are produced by the liver), and bilirubin (a measure of the liver's detoxifying ability). Collectively all the above tests are a measure of liver function, however the liver

enzymes AST, ALT, AP, and GGT are commonly referred to as liver function tests (LFTs) in the medical field. In this article, we will discuss the evaluation of patients with elevated liver enzymes, which we will be referring to as LFTs for the rest of this article.

Many screening test panels now routinely include LFTs, and as a result, abnormal values (>2 standard deviations above normal, often >55IU/L) are frequently detected in non-symptomatic patients. 5% of healthy individuals who have a single screening test will have an abnormal result. A population-based survey in the United States conducted between 1999-2002 estimated that an abnormal ALT was present in 8.9% of individuals. This may be related to the increase in obesity that has also occurred during the same period, since ALT correlates with body mass index and waist circumference. There are many studies that evaluate the clinical significance of finding elevated LFTs on a routine blood test, and most of them show that it is uncommon to find a serious underlying liver disease, especially if the patient does not have risk factors for liver disease (alcohol abuse, unsafe sex, intravenous and intranasal drug abuse, blood transfusion before 1990, tattoos, certain medications such as Tylenol, liver toxins). A diagnosis can be established non-invasively in the majority of patients with abnormal LFTs, including appropriate history and physical exam of the patient. If diagnosis after non-invasive tests is still unclear, further testing can be guided by liver biopsy, which is the most critical test that leads to proper diagnosis and treatment of liver disease.

The most important part in evaluating patients with elevated LFTs is completing a full medical history. The presence of any one or more of the symptoms discussed above should be documented. Moreover, the pattern of the symptoms may suggest a certain diagnosis; a history of joint/muscle pain preceding jaundice usually goes more with viral or drug related hepatitis, whereas jaundice associated with sudden onset severe right upper quadrant abdominal pain plus shaking chills suggest stones in the bile ducts with or without infection. Medication history, including prescription, over the counter, and herbal therapies are also important information. The use of illicit drugs, or exposure to any chemical should also be noted. Duration of LFTs elevation differentiates a single non-significant abnormal finding from chronic elevation (>6 months) which usually signifies an underlying illness. Any information collected can help doctors pinpoint the diagnosis with more accuracy, thus narrowing the array of tests that need to be done.

Next is physical examination, where doctors look for stigmata that will further guide the diagnosis. The patient's overall condition is vital. Patients who look ill, emaciated, with muscle wasting will most likely have a significant long standing illness. The skin is examined for any jaundice, rashes, or red blanching spots called spider nevi which are characteristic of liver disease. The neck is examined for any distended veins which can imply liver congestion. Lymph node locations are palpated to check for any enlargement that would suggest cancer. The lungs are auscultated for any decreased breath sounds which can be due to pleural effusion that may be seen in advanced cirrhosis. Abdominal exam should be focused. The abdomen is inspected for any distention which could be from excess fluid (ascites), and for the presence of dilated veins (called caput medusa because the veins bear a resemblance to the head of Greek mythology character medusa), and these two findings usually occur in cirrhosis. Excess fluid can be further evaluated by performing special exam maneuvers, such as dullness upon

percussion of the abdomen, or checking for a fluid wave. Palpation of the abdomen is performed to assess for liver enlargement, which could result from malignancy, viral, or alcoholic hepatitis. Tender spots could be due to gall bladder stones obstructing the bile ducts, especially if the right upper abdominal quadrant becomes severely tender with inspiration.

Summing up all information obtained from history and physical exam, doctors generally create a list of differential diagnosis to explain the findings, and based on that list, an array of tests are usually ordered if needed, either to increase the accuracy or confirm a certain diagnosis. The pattern of LFT elevation should first be noted, as a ratio of AST:ALT >2:1 is most likely due to alcohol abuse, and thus stopping alcohol intake should decrease LFTs unless liver injury was at an irreversible stage. A ratio <1 is usually due to fatty liver, and that is evaluated by an abdominal ultrasound, which can be followed with liver biopsy if worsening or no improvement. A hepatitis panel can be requested if index of suspicion for viral infection is high. This includes hepatitis A antibody; hepatitis C antibody plus viral load; hepatitis B surface antigen and antibody, core antibody, viral load, with or without its “e” antigen and antibody which informs us of the infectivity of the virus (highly infective if hepatitis Be antigen positive, and thus worse outcome). Iron level plus ferritin (which is the iron storage form) are measured to screen for iron overload (hemochromatosis). Less common causes include autoimmune hepatitis, especially if history is positive for other autoimmune diseases, and screening is performed with anti-nuclear antibody (ANA) and anti-smooth muscle antibody (SMA). Wilson’s disease (excess copper) is another uncommon cause and we screen with copper and ceruloplasmin levels in the blood (ceruloplasmin binds copper and helps in its excretion from the body, and is low in Wilson’s disease). Another rare cause of liver disease is alpha-1-antitrypsin deficiency, considered especially in non-smoking patients who have associated lung emphysema and screening is done with genetic studies. Elevated LFTs can also be due to non-liver causes, which should be accounted for if all the liver studies are non-revealing. These include thyroid disorders (check with thyroid hormone levels T4 and T3, and TSH), muscle disorders (check creatine kinase), adrenal insufficiency (check cortisol level), and celiac disease (check tissue trans-glutaminase antibody).

Finally, a liver biopsy is the last step in the algorithm for working up patients with elevated LFTs. After review of the liver biopsy and putting together all pieces of information into one diagnosis, a proper treatment program and follow up plans are instituted by the doctor.

“THE LIVER IS A VITAL ORGAN AND SHOULD BE GIVEN UTMOST RESPECT”