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THE IMPORTANCE OF LABORATORY RESULTS IN THE TREATMENT OF LIVER DISEASE

Raxmonov Shoxzodbek Oybek o'g'li
Assistant of the Department of Pathology and
Forensic Medicine, Central Asian Medical University
Andijan State Medical Institute, 2 nd year clinical supervisor,
"Laboratory work" course

Annotation

Chronic liver disease is a progressive deterioration of liver functions. Liver functions include the production of clotting factors and other proteins, detoxification of harmful products of metabolism, and excretion of bile. This is a continuous process of inflammation, destruction, and regeneration of liver parenchyma leading to fibrosis and cirrhosis. Cirrhosis is a final stage of chronic liver disease that results in disruption of liver architecture, the formation of widespread nodules, vascular reorganization, neo-angiogenesis, and deposition of an extracellular matrix. The underlying mechanism of fibrosis and cirrhosis at a cellular level is the recruitment of stellate cells and fibroblasts that cause fibrosis, while parenchymal regeneration relies on hepatic stem cells.

Key words: alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), serum bilirubin, prothrombin time (PT), the international normalized ratio (INR)

Chronic liver disease (CLD) is a progressive deterioration of liver functions for more than six months, which includes synthesis of clotting factors, other proteins, detoxification of harmful products of metabolism, and excretion of bile. CLD is a continuous process of inflammation, destruction, and regeneration of liver parenchyma, which leads to fibrosis and cirrhosis. The spectrum of etiologies is broad for chronic liver disease, which includes toxins, alcohol abuse for a prolonged time, infection, autoimmune diseases, genetic and metabolic disorders. Cirrhosis is a final stage of chronic liver disease that results in disruption of liver architecture, the formation of widespread nodules, vascular reorganization, neo-angiogenesis, and deposition of an extracellular matrix. The underlying mechanism of fibrosis and cirrhosis at a cellular level is the recruitment of stellate cells and fibroblasts, resulting in fibrosis, while parenchymal regeneration relies on hepatic stem cells. Chronic liver disease is an extremely common clinical condition, and the focus is done on the common etiologies, clinical manifestations, and management.

Pathophysiology of liver disease:

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Chronic liver disease represents a continuous and progressive process of hepatic fibrosis, liver tissue architectural distortion, and regeneration nodule formation. While fibrosis is usually irreversible, but it can be reversible in the initial stage of development. The transition time point of reversible fibrosis to irreversible fibrosis is still not completely understood. In chronic liver disease, if not treated, the endpoint is usually irreversible fibrosis, regeneration nodule formation, and development of cirrhosis liver. The development rate of fibrosis is dependent on the underlying etiologies, environmental, and host factors. The rate was most rapid in patients with coinfection with HIV- HCV, while primary biliary cirrhosis was the slowest. Fibrosis progression rate was higher with increasing age, and females demonstrated a more gradual progression of liver fibrosis in all but alcoholic liver disease. Similarly, in another study, genetic polymorphism was attributed as an underlying factor for the difference in fibrosis rate progressions and the development of more severe disease in some individuals compared to others with the same underlying etiology. Hepatic fibrosis is the deposition of extracellular matrix (ECM) in response to chronic liver injury by any etiology. The common pathway is initiated by hepatic stellate cells (HSC), which usually are vitamin A storing dormant cells found in space between sinusoids and hepatocytes. In response to chronic liver injury, HSC gets activated into proliferative fibrogenic myofibroblast and upregulates the expression of inflammatory receptors such as chemokine receptors, ICAM-1, and other inflammatory mediators by releasing chemokines and other leukocyte chemoattractants. This pro-inflammatory phase or initiation phase also changes gene and phenotypic expression of the liver cells, making them more responsive to these inflammatory cytokines, and perpetuation of activated HSC cells results in the accumulation of ECM and progressive fibrosis.

Lobaratory findings:

The liver has a significant role in metabolism, digestion, detoxification, and elimination of substances from the body. The liver function tests typically include alanine transaminase (ALT) and aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), serum bilirubin, prothrombin time (PT), the international normalized ratio (INR), total protein and albumin. These tests can help determine an area of the liver where damage may be taking place and, depending on the pattern of elevation, can help organize a differential diagnosis. Elevations in ALT and AST disproportion to elevations in alkaline phosphatase and bilirubin denote hepatocellular disease. An elevation in alkaline phosphatase and bilirubin in disproportion to ALT and AST would characterize a cholestatic pattern. The actual function of the liver can be graded based on its ability to produce albumin as well as vitamin K-dependent clotting factors.

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Elevated liver function tests are found in approximately 8% of the general population. These elevations may be transient in patients without symptoms, with up to 30% of elevations resolving after three weeks. Thus, care should be taken when interpreting these results to avoid unnecessary testing. A borderline AST and/or ALT elevation is defined as less than 2 times the upper limit of normal (ULN), a mild AST and/or ALT elevation as 2 to 5 times ULN, moderate AST and/or ALT elevation 5 to 15 times ULN, severe AST and/or ALT elevation greater than 15 times ULN, and massive AST and/or ALT greater than 10,000 IU/l.The magnitude of AST and ALT elevation varies depending on the cause of hepatocellular injury.

Hepatocellular pattern: Elevated aminotransferases out of proportion to alkaline phosphatase

ALT-predominant: Acute or chronic viral hepatitis, steatohepatitis, acute Budd-Chiari syndrome, ischemic hepatitis, autoimmune, hemochromatosis, medications/toxins, autoimmune, alpha1-antitrypsin deficiency, Wilson disease, Celiac disease

AST-predominant: Alcohol-related, steatohepatitis, cirrhosis, non-hepatic (hemolysis, myopathy, thyroid disease, exercise)

Cholestatic pattern: Elevated alkaline phosphatase +gamma glutamyl transferase + bilirubin out of proportion to AST and ALT

Hepatobiliary causes: Bile duct obstruction, primary biliary cirrhosis, primary sclerosing cholangitis, medication-induced, infiltrating diseases of the liver (sarcoidosis, amyloidosis, lymphoma, among others), cystic fibrosis, hepatic metastasis, cholestasis

Non-Hepatic causes: Bone disease, pregnancy, chronic renal failure, lymphoma or other malignancies, congestive heart failure, childhood growth, infection, or inflammation.

Components of Liver Function Test

Hepatocellular Labs

Aminotransferase includes AST and ALT. They are markers of hepatocellular injury. They participate in gluconeogenesis by catalyzing the transfer of amino groups from aspartic acid or alanine to ketoglutaric acid to produce oxaloacetic acid and pyruvic acid, respectively. AST is present as cytosolic and mitochondrial isoenzymes and is found in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leucocytes, and red cells. It is not as sensitive or specific for the liver as ALT and elevation in AST may be seen as secondary to nonhepatic causes as well. AST activity in neonates and infants is approximately twice that in adults, but these decline to adult levels by approximately six months. ALT is a cytosolic enzyme that is found in high concentrations in the liver. The half-life of ALT is approximately 47 ± 10 hours. ALT is usually higher than AST in most types of liver disease in which the activity of both enzymes is

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predominantly from the hepatocyte cytosol. Hepatocellular injury and not necessarily cell death triggers the release of these enzymes into circulation. Both AST and ALT values are higher in normal males than females.[8]They also correlate with obesity with a normal reference range higher in those with higher body mass index.[9]

Cholestasis Labs

Alkaline phosphatase is part of a family of zinc metalloenzymes that are highly concentrated in the microvilli of the bile canaliculus as well as several other tissues (e.g., bone, intestines, and placenta). There are four isozymes: placental ALP or hPLALP (human placental ALP), germ cell ALP (GCALP or PLALP-like), intestinal ALP (IALP), and tissue-nonspecific ALP (TNALP). Of these four, PLALP and GCALP are the most heat stable at 65 C, and the bone ALP component of TnALP is the least. In healthy, non-smoking individuals, the PLALP and GCALP represent less than 1% of total ALP activity in the serum. A condition that can result in significantly increased plasma ALP is benign transient hyperphosphatasemia. Originally described in infants, transient hyperphosphatasemia can also occur in adults and during pregnancy. There is a marked rise in ALP, often to several thousand IU/L, which usually indicates significant pathology. It is, however, a benign condition with a return to normal of the ALP in 6 to 8 weeks. Transient hyperphosphatasaemia is associated with concurrent infections in over 60% of cases, particularly GIT infections. There is a characteristic pattern on polyacrylamide gel electrophoresis, with the normal pattern of isoenzymes being accompanied by variant forms that react with neuraminidase. It is believed to be due to changes in carbohydrate side chains causing failure of recognition by receptors and reduced clearance, thus prolonging half-life.

Glycoprotein gamma-glutamyltransferase (GGT) is located on membranes of cells with high secretory or absorptive activities. Its primary function is to catalyze the transfer of a gamma-glutamyl group from peptides to other amino acids. It is also abundant in many other sources of the body (kidney, pancreas, intestine, prostate, testicles, spleen, heart, and brain) but is more specific for biliary disease when compared to alkaline phosphatase because it is not present in bone. Serum GGT shows electrophoretic mobility and lectin-affinity reaction identical to the liver enzyme but different from GGT from the kidney, urine, and pancreas.GGT levels are reported to be increased by an average of 12-fold in obstructive liver disease compared to ALP, which increased only 3-fold, so GGT is slightly more sensitive than ALP in this regard.GGT activity level in children may be a reliable index of bile duct damage. It is a useful indicator in separating the two forms of idiopathic cholestasis, with or without bile duct involvement. In infants diagnosed

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with biliary atresia and managed surgically, the GGT levels stay high in the blood if the infant is breastfed. This is due to the high level of GGT in human breast milk for at least four weeks postpartum.

There is a relationship between plasma GGT activity and weight, with values being 50% higher in individuals with a BMI greater than 30 kg/m2. This is believed to be due to fat deposition in the liver (steatosis) in obese subjects. Steatosis with a raised plasma GGT also occurs in diabetes mellitus, non-alcoholic steatohepatitis, and non-alcoholic fatty liver disease. Any liver disease that results in fibrosis and/or cirrhosis, such as alcoholic cirrhosis, PBC, PSC, hemochromatosis, α1-antitrypsin deficiency, and Wilson disease, will cause a raised plasma GGT. Space-occupying lesions, including malignancy (HCC or metastases secondary to malignancy elsewhere in the body), and granulomatous disease, for example, sarcoidosis and TB, are also associated with a raised plasma GGT.5′-Nucleotidase (5′NT) is associated with the canalicular and sinusoidal plasma membranes. Its function is undefined. 5′NT is also found in the intestine, brain, heart, blood vessels, and endocrine pancreas. Serum levels of 5′NT are unaffected by sex or race, but age affects the level; values are lowest in children and increase gradually, reaching a plateau at approximately age 50 years. As with GGT, the primary role of the serum 5′NT level is to identify the organ source of an isolated serum alkaline phosphatase elevation. The 5′NT level is not increased in bone disease but primarily in hepatobiliary disease. LDH is commonly included in biochemical liver panels but has poor diagnostic specificity for liver disease. Markedly increased LDH levels are observed in hepatocellular necrosis, shock liver, lymphoma, or hemolysis associated with liver disease.

Bilirubin is the end product of heme catabolism, with 80% derived from hemoglobin. Unconjugated bilirubin is transported to the liver loosely bound to albumin. Bilirubin is water-insoluble and cannot be excreted in the urine. Bilirubin that is conjugated is water-soluble and appears in the urine. It is conjugated in the liver to bilirubin glucuronide and subsequently secreted into bile and the gut, respectively.

Synthetic Function Tests

Albumin is synthesized by the hepatic parenchymal cells at a rate dependent on colloidal osmotic pressure and dietary protein intake. The rate of albumin synthesis is also subject to feedback regulation determined by the plasma albumin concentration. Maintenance of plasma albumin concentrations can be achieved with only 10% of normal hepatocyte mass. The half-life of albumin is 21 days. Traces of albumin can be found in almost all extracellular body fluids. Little is lost from the body by excretion. It is catabolized in various tissues, which are taken up by cells

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by pinocytosis. Its constituent amino acids are released by intracellular proteolysis and returned to the body pool. With any liver disease, there is a fall in serum albumin, reflecting decreased synthesis. If liver function is normal and serum albumin is low, this may reflect poor protein intake (malnutrition) or protein loss (nephrotic syndrome, malabsorption, or protein-losing enteropathy).

Prothrombin time (PT) measures the rate of conversion of prothrombin to thrombin. Except for factor VIII, all other coagulation factors are synthesized by the liver. Prothrombin time requires factors II, V, VII, and X, and, as these are made in the liver, the liver's function is crucial in coagulation. Suppose the synthetic function of the liver is normal and prothrombin time is delayed. This may indicate treatment with warfarin, consumptive coagulopathy (eg, disseminated intravascular coagulopathy), or vitamin K deficiency.

Serological Tests

Liver-related autoantibodies are crucial for correctly diagnosing and classifying autoimmune liver diseases, namely autoimmune hepatitis types 1 and 2 (AIH-1 and 2), primary biliary cirrhosis (PBC), and the sclerosing cholangitis variants in adults and children.AIH-1 is specified by anti-nuclear antibody (ANA) and smooth muscle antibody (SMA). AIH-2 is specified by antibody to liver kidney microsomal antigen type-1 (anti-LKM1) and anti-liver cytosol type 1 (anti-LC1). SMA, ANA, and anti-LKM antibodies can be present in de-novo AIH following liver transplantation.[18]PBC is specified by antimitochondrial antibodies (AMA) reacting with enzymes of the 2-oxo-acid dehydrogenase complexes (chiefly pyruvate dehydrogenase complex E2 subunit) and disease-specific ANA mainly reacting with nuclear pore gp210 and nuclear body sp100. Sclerosing cholangitis presents in at least two variants; first, the classical primary sclerosing cholangitis (PSC) mostly affects adult men wherein the only (and non-specific) reactivity is an atypical perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA), also termed perinuclear anti-neutrophil nuclear antibodies (p-ANNA) and second the childhood disease called autoimmune sclerosing cholangitis (ASC) with serological features resembling those of type 1 AIH.

Secondary Biochemical Liver Tests

Alpha-fetoprotein (AFP) measurements are used as a tumor marker for the detection and monitoring of primary hepatocellular malignancies, such as hepatoblastoma and HCC. Hepatoblasts produce alpha-fetoprotein, which is why it is raised in the regenerating liver, particularly in chronic viral hepatitis.

Carbohydrate deficient transferrin is a high-specificity test for detecting excess alcohol intake as a cause of liver damage. The carbohydrate antigen CA19-9 is useful in monitoring the

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activity of the autoimmune disease PSC, which often progresses to a tumor of the bile ducts or cholangiocarcinoma. Measurement of serum ferritin can be useful in identifying hemochromatosis, but ferritin is a positive acute phase reactant, so it is raised in many illnesses as well as being released from damaged hepatocytes in acute hepatic failure.

Specimen Requirements and Procedure

The serum is the specimen of choice. Consider all plasma or serum specimens potentially positive for infectious agents, including HIV and the hepatitis B virus. All specimens should be handled with standard precautions and sent to the lab immediately for processing. Separated serum or plasma should not remain at +15 C to +30 C longer than 8 hours. If assays are not completed within 8 hours, serum or plasma should be stored at +2 C to +8 C. If assays are not completed within 48 hours, or the separated sample is to be stored beyond 48 hours, samples should be frozen at –15 C to –20 C. Frozen samples should be thawed only once. Analyte deterioration may occur in samples that are repeatedly frozen and thawed.

Testing Procedures

Liver function tests are performed on semi-automatic or fully automated analyzers, which are based on the principle of photometry. Photometry is the measurement of light absorbed in the ultraviolet (UV) to visible (VIS) to infrared (IR) range. This measurement is used to determine the amount of an analyte in a solution or liquid. Photometers utilize a specific light source and detectors that convert light passed through a sample solution into a proportional electrical signal. These detectors may be photodiodes, photoresistors, or photomultipliers. Photometry uses Beer–Lambert's law to calculate coefficients obtained from the transmittance measurement. A correlation between absorbance and analyte concentration is then established by a test-specific calibration function to achieve highly accurate measurements.

Conclusion, Liver function tests are one of the most commonly ordered laboratory tests. Mild isolated elevations in LFTs can be seen as normal fluctuations and shall not trigger expensive and extensive workups. However, clinicians shall be aware of various conditions that can lead to an elevation in LFTs. Thorough history taking and physical examination can provide clues to the differential diagnosis.

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