Approach to Patients with Increased Liver Biochemical and Function Tests : A Literature Review

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ABSTRACT

This review article provides a comprehensive examination of liver injury patterns, specifically focusing on hepatocellular and cholestatic patterns, and their respective diagnostic approaches. It highlights the importance of differentiating between these patterns through detailed clinical evaluations and the use of specific liver enzymes, including aminotransferases, bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase, 5'-nucleotidase, and lactate dehydrogenase. The review further explores liver function tests, such as albumin and prothrombin time, which are crucial in assessing liver function and guiding clinical management. A wide range of liver diseases is discussed, with a focus on those exhibiting hepatocellular patterns, such as viral hepatitis, acute liver failure, fatty liver disease (both alcoholic and non-alcoholic), and drug-induced liver injury (DILI), as well as other conditions like ischemic and autoimmune hepatitis. Cholestatic illnesses such as primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), bile duct blockages, and genetic cholestatic syndromes are also investigated. This study seeks to improve physicians' and researchers' awareness of liver diseases, serve as a valuable resource for future research and teaching, and contribute to the improvement of diagnostic and therapeutic techniques in hepatology.

Keywords : *cholestatic, hepatocellular, liver enzymes, liver functions*

ABSTRAK

Artikel ulasan ini memberikan pemeriksaan yang komprehensif tentang pola penyakit liver, khususnya dengan fokus pada pola hepatoseluler dan kolestatik, serta pendekatan diagnostik masing-masing. Artikel ini menyoroti pentingnya membedakan antara pola-pola ini melalui evaluasi klinis yang rinci dan penggunaan enzim liver tertentu, termasuk aminotransferase, bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase, 5'-nukleotidase, dan lactate dehydrogenase. Ulasan ini juga menjelaskan tes fungsi liver, seperti albumin dan waktu protrombin, yang penting dalam menilai fungsi liver dan membimbing manajemen klinis. Berbagai penyakit hati dibahas, dengan fokus pada penyakit yang menunjukkan pola hepatoseluler, seperti hepatitis virus, gagal liver akut, fatty liver (baik alkoholik maupun non-alkoholik), dan drug induced liver injury (DILI), serta kondisi lain seperti hepatitis iskemik dan autoimun. Penyakit kolestatik seperti kolangitis bilier primer (PBC), kolangitis sklerosis primer (PSC), penyumbatan saluran empedu, dan sindrom kolestatik genetik juga diselidiki. Studi ini bertujuan untuk meningkatkan kesadaran dokter dan peneliti tentang penyakit liver, menjadi sumber yang berharga untuk penelitian dan pengajaran di masa depan, dan berkontribusi pada peningkatan teknik diagnostik dan terapeutik dalam hepatologi.

Kata kunci: *enzim liver, fungsi liver, hepatoseluler, kolestatik*

INTRODUCTION

Considering the frequency of liver illnesses around the world, early and accurate detection via a comprehensive strategy is essential for successful care. Abnormal liver test results are frequently caused by diseases such as cirrhosis, fatty liver disease, and hepatitis. Comprehending the clinical consequences of these irregularities facilitates the direction of diagnostic and treatment methodologies, ultimately leading to enhanced patient results.[1]

In medical practice, the term "liver function tests" (LFTs) is frequently used, yet it can be deceptive because many tests in this category do not evaluate liver function directly. Rather, they assess particular blood chemicals and enzymes to gauge liver damage or inflammation. While these tests offer valuable insights into the health of the liver, they may not accurately represent the liver's true functional capacity. Liver cell injury is indicated by liver enzymes such as 5' nucleotidase, gamma-glutamyl transferase (GGT), bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT). On the other hand, liver function tests, such as prothrombin time (PT) and serum albumin, evaluate the liver's excretory and synthetic capacities.[2,3]

HEPATOCELLULAR VS CHOLESTATIC PATTERNS

It is essential to recognize the differences between cholestatic and hepatocellular patterns in order to diagnose and treat liver disorders. Cholestatic injury affects the bile ducts and bile flow, whereas hepatocellular injury largely affects liver cells. Clinical characteristics and specific liver enzyme abnormalities set these patterns apart. Hepatocytes that have been injured release aminotransferases, especially alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which are primarily elevated in hepatocellular patterns.[4] Whereas AST is also present in cardiac and skeletal muscle, ALT is more unique to the liver[2]. Hepatocellular injuries, including drug-induced liver injury, alcoholic liver disease, and viral hepatitis, are frequently associated with elevated ALT-to-AST ratios.[5] Histologically, hepatocyte necrosis and inflammation are frequently observed in liver biopsies.[6]

On the other hand, cholestatic patterns are distinguished by increased bile duct-associated enzyme levels of gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP).[7] These elevations indicate impaired bile flow, which can result from intrahepatic causes like primary biliary cholangitis or extrahepatic causes such as bile duct obstruction due to gallstones or tumors.[8] Clinically, cholestasis may present with jaundice, pruritus, and dark urine.[9] A liver biopsy in cholestatic conditions typically reveals bile duct injury and cholestasis.[6]

The ratio of ALT to ALP, or the R factor, is a useful diagnostic tool for distinguishing between these forms of liver injury. A cholestatic pattern is indicated by a R factor less than 2, whereas a hepatocellular pattern is suggested by a R factor more than 5. A heterogeneous pattern of liver damage is indicated by values ranging from 2 to 5.[2] Distinguishing between these patterns is crucial for focused diagnostic examinations and remedial measures. For example, serological testing aids in the diagnosis of autoimmune liver disorders and viral hepatitis in cases with hepatocellular damage, while imaging procedures such as MRI cholangiopancreatography or ultrasound are useful in determining cholestatic causes.[7] Patient outcomes are improved and treatment techniques are more effective when these patterns are accurately and promptly distinguished.[8]

Further Diagnostic Approaches

When evaluating individuals who have elevated liver biochemistry and function tests, the evaluation of liver function tests (LFTs), such as serum albumin and prothrombin time, is crucial. Even though LFTs are frequently utilized in clinical settings, it's crucial to understand that while they may not be able to measure liver function directly, they can nevertheless offer insightful information about liver health. Reduced levels of serum albumin, which are frequently observed in chronic liver illness, indicate diminished capacity for the liver's synthetic function. On the other side, prothrombin time evaluates the liver's excretory capacity; a prolonged value suggests compromised hepatic synthetic function. Comprehending the importance of these tests facilitates the identification of underlying liver pathology and directs additional diagnostic assessment.[10]

Imaging methods are also essential for differentiating between cholestatic and hepatocellular liver diseases in addition to liver function testing.[11] Ultrasonography is a widely used imaging modality because it is affordable, safe, and readily available. It is capable of identifying characteristics that point to hepatic injury, such as localized lesions and abnormalities of the liver parenchyma, as well as indications of

cholestatic disorders such as biliary dilatation or blockage. Both magnetic resonance imaging (MRI) and computed tomography (CT) provide precise anatomical information and are especially useful for evaluating liver vascularity and defining liver abnormalities.[12] Transient elastography is a non-invasive technique that helps with disease staging and surveillance by evaluating liver fibrosis.[13]

While invasive, liver biopsy provides invaluable information regarding liver histology, allowing for accurate differentiation between cholestatic and hepatocellular patterns. Histopathological examination reveals characteristic features such as bile duct proliferation and injury in cholestatic diseases, while hepatocellular injuries are characterized by hepatocyte necrosis and inflammation. Despite its invasiveness, liver biopsy is still the gold standard in the diagnostic armamentarium for liver disorders, guiding therapeutic decisions and optimizing patient care.[5]

LIVER ENZYMES

Liver enzymes are biochemical substances produced by the liver cells (hepatocytes) that are released into the bloodstream under various conditions, reflecting liver health and function. Abnormal levels of these enzymes can indicate liver injury or dysfunction, providing valuable diagnostic information.

Aminotransferases (AST/ALT)

Aminotransferase, or ALT and AST, is a type of enzyme involved in amino acid metabolism. In people without known risk factors for liver disease, the normal range for men's ALT levels is 29-33 IU/L and for women's ALT levels is 19-25 IU/L. However, the average AST level for men and women is 14-20 units/L and 10-36 units/L, respectively. The liver contains the greatest levels of ALT. Unlike ALT, AST can be found in a wide range of tissues.[14]

ALT is mainly responsible for catalyzing the conversion of pyruvate and glutamate from alanine and α-ketoglutarate, whereas AST facilitates the reversible transfer of an amino group from aspartate to α-ketoglutarate. When hepatocellular integrity is damaged, these enzymes, which are prevalent in hepatocytes, are discharged into the bloodstream. When hepatocellular injury is caused by illnesses including viral hepatitis, drug-induced liver injury, alcoholic liver disease, or non-alcoholic fatty liver disease (NAFLD), elevated levels of ALT and AST are frequently seen. In cases of hepatocellular damage, the degree of ALT elevation is frequently higher than AST, leading to an elevated ALT-to-AST ratio that can help differentiate between various liver illnesses.[15,16]

Bilirubin

Bilirubin is produced when heme, a hemoglobin component found in red blood cells, is broken down. After bilirubin passes through the bloodstream coupled to albumin, hepatocytes in the liver react it with glucuronic acid to form conjugated bilirubin. This conjugated bilirubin, which dissolves in water, can be removed through bile excretion. Total bilirubin concentrations in the blood typically vary from 0.1 to 1.2 mg/dL. Within this range, the typical amounts of direct (conjugated) and indirect (unconjugated) bilirubin are 0 to 0.3 mg/dL and 0.2 to 0.9 mg/dL, respectively. The laboratory standards being used may create minor deviations in these ranges.[16]

Elevated levels of bilirubin in the bloodstream can occur due to various reasons, including increased production (such as in hemolysis), impaired hepatic uptake or conjugation (as seen in hepatocellular dysfunction), or obstructed bile flow (cholestasis). Serum bilirubin levels are usually high in cholestatic liver illnesses or bile duct obstruction. These increases are frequently accompanied by elevated levels of alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT), indicating decreased bile flow and cholestasis.[16,17]

Alkaline Phosphatase (ALP)

The enzyme alkaline phosphatase (ALP) is present in the liver, bile ducts, bones, and placenta, among other tissues in the body. Dephosphorylation, the process of removing phosphate groups from molecules, is a critical step in a number of metabolic processes, and it entails the involvement of ALP. ALP levels in the blood might vary according to factors including age, gender, and pregnancy status, but in adults, the normal range is typically 44–147 IU/L. Because of bone growth, higher levels may be typical in children and adolescents. Cholangiocytes, the cells that line the bile ducts, are the main producers of ALP; hepatocytes generate it to a lower degree. Additionally, osteoblasts in bone make it, and the placenta is a major source of ALP during pregnancy. Conditions affecting the liver, bile ducts, or bones can cause elevated ALP levels. Elevated ALP in the liver is frequently linked to cholestatic liver diseases [(18)]. Though less frequently, it can also be raised in hepatocellular disorders. Elevated

ALP levels can also be a symptom of bone disorders, including osteomalacia, Paget's disease, and bone metastases.[19]

Gamma-glutamyl transpeptidase (GGT)

The enzyme known as gamma-glutamyl transpeptidase (GGT) is essential to the liver's detoxification activities and glutathione metabolism. It facilitates the transfer of gamma-glutamyl functional groups. GGT levels in blood normally range from 9 to 48 IU/L, though this could change slightly according on the laboratory standards being utilized. The cells that line the bile ducts in the liver are the primary source of GGT. Additionally, the pancreas, intestines, and kidneys contain it. Diseases of the liver and bile duct frequently cause elevated GGT levels. It is particularly sensitive to obstruction of the bile duct and is frequently raised in alcoholic liver disease and cholestatic liver illnesses [(20)]. Elevated GGT levels in conjunction with elevated ALP levels strongly suggest cholestasis or bile duct pathology.[21]

5'-nucleotidase (5'-NT)

5'-Nucleotidase (5'-NT) is responsible for hydrolyzing nucleotides into nucleosides and inorganic phosphate. It is mostly located in the bile canaliculi of the liver and is involved in the metabolism of nucleotides. 5'-NT in blood normally ranges from 2 to 17 units/L, however this can change based on laboratory standards. The primary producers of 5'-NT are hepatocytes and the cells lining the bile ducts. Though in far smaller amounts, it is also found in the brain, heart, and intestines, among other tissues. The most common association between elevated 5'-nucleotidase levels and liver disorders is cholestasis. It is a sensitive marker for primary sclerosing cholangitis, primary biliary cholangitis, and obstruction of the bile duct. Elevated 5'-nucleotidase levels indicate impaired bile flow and can help differentiate between hepatocellular and cholestatic liver diseases. Unlike alkaline phosphatase (ALP), 5'-nucleotidase is not significantly elevated in bone diseases, making it a more specific marker for liver-related pathology.[22,23]

Lactate dehydrogenase (LDH)

Lactate dehydrogenase (LDH) is involved in the glycolysis process, which turns lactate into pyruvate. It is found in nearly every bodily tissue, but is most concentrated in the heart, liver, muscles, kidneys, and lungs. Although this range can vary slightly depending on the laboratory and the assay utilized, the normal range for LDH in the blood is normally 140 to 280 units/L. The body produces five distinct isoenzymes of LDH, each of which is distributed differently across the body's tissues. The liver and skeletal muscles are the main locations of LDH-5. Many illnesses that induce tissue damage and cell lysis can have elevated LDH levels. Due to its lack of specificity, LDH is often used in conjunction with other tests to diagnose and monitor liver and other diseases.[24,25]

LIVER FUNCTION TESTS

Albumin

Albumin is an essential plasma protein produced only by the liver. It acts as a carrier protein for a variety of compounds, including hormones, fatty acids, and pharmaceuticals, and is critical in controlling oncotic pressure, which retains fluid in blood vessels. The typical range for serum albumin levels is 3.5 to 5.0 g/dL. Albumin is produced by hepatocytes and is influenced by a variety of factors such as hormonal balance, nutrition, and the presence of inflammatory cytokines.[26]

Elevated albumin levels are not clinically significant and are rather uncommon. Low albumin levels (hypoalbuminemia) are increasingly common and can be indicative of a variety of medical conditions. Cirrhosis and chronic hepatitis, which impair the liver's capacity to manufacture hepatocytes, can cause hypoalbuminemia. Nephrotic syndrome, chronic inflammatory diseases, malnutrition, and malabsorption syndromes are among the other causes. Low albumin levels can lead to edema and ascites as oncotic pressure decreases.[27]

Prothrombin Time (PT)

The prothrombin time (PT) measures the time it takes for blood to clot. Because the liver produces the bulk of clotting factors, it evaluates the extrinsic pathway of coagulation and is commonly used to examine the liver's synthetic function. PT typically varies from 11 to 13.5 seconds, while actual results may vary greatly depending on the lab and the substances used. The International Normalized Ratio (INR), with a typical range of 0.8 to 1.2, is a popular way to express PT.[28]

In liver illnesses such cirrhosis and acute liver failure, when the synthesis of these factors is compromised, PT is prolonged when there is a deficit of clotting factors. Another cause of prolonged PT

is a vitamin K shortage, which is required for the synthesis of several clotting components. In patients with liver illness, elevated PT/INR levels are used to monitor anticoagulant medication and evaluate liver function since they are associated with an increased risk of bleeding.[29]

DISEASES WITH HEPATOCELLULAR PATTERN

Viral Hepatitis

Hepatitis virus infections are the primary cause of substantial hepatic injury in viral hepatitis. These viruses cause inflammation, necrosis, and varied degrees of liver cell damage when they attack hepatocytes. The capacity of hepatitis B (HBV) and hepatitis C (HCV) to induce chronic liver disease makes them stand out among the others. HCV mainly spreads by blood-to-blood contact, whereas HBV is disseminated through blood, sexual contact, and perinatal pathways. The symptoms of an acute infection might range from moderate exhaustion to severe jaundice and liver damage. If treatment for chronic HBV and HCV infections is not received, the virus's continued reproduction and immune system-mediated hepatocyte destruction cause persistent inflammation and fibrosis, which can eventually lead to cirrhosis and hepatocellular cancer.[30]

Chronic HBV and HCV infections are significant risk factors for this liver cirrhosis. As these infections progress to cirrhosis, a mixed pattern of liver injury with both hepatocellular and cholestatic characteristics often replaces the primarily hepatocellular pattern. To minimize major liver damage, early detection and treatment are critical, as this varied injury pattern complicates therapeutic management.[30,31]

Fatty Liver

There are two possible causes of fatty liver disease: alcohol and non-alcoholic substances. Overindulgence in alcohol causes fatty liver disease (AFLD), which is characterized by hepatocyte fat buildup and hepatocellular damage. Alcohol metabolism in the liver results in the production of harmful byproducts such reactive oxygen species and acetaldehyde, which lead to oxidative stress, lipid peroxidation, and mitochondrial dysfunction. These mechanisms result in fibrosis, necrosis, and inflammation, all of which are indicative of a hepatocellular damage pattern. If chronic alcohol use is not treated, it can lead to cirrhosis and hepatocellular cancer from simple steatosis (fatty liver) to alcoholic hepatitis.[32]

Conversely, non-alcoholic fatty liver disease (NAFLD) refers to a group of liver illnesses that are not caused by excessive alcohol consumption, such as non-alcoholic steatosis and non-alcoholic steatohepatitis (NASH). Obesity, insulin resistance, type 2 diabetes, dyslipidemia, and metabolic syndrome are all associated with nonalcoholic fatty liver disease (NAFLD). Excess lipids in the liver induce hepatocellular injury in nonalcoholic fatty liver disease (NAFLD), which is accompanied by oxidative stress, inflammatory cytokine release, and mitochondrial dysfunction. The progression from basic steatosis to nonalcoholic steatosis (NASH) involves further inflammation, hepatocyte ballooning, and fibrosis, resulting in a hepatocellular pattern of liver damage. NAFLD can progress to cirrhosis and hepatocellular carcinoma if not treated.[33]

Drug – Induced Liver Injury (DILI)

Drug-induced liver damage (DILI) occurs when certain medicines, herbal supplements, or other compounds affect the liver, resulting in hepatocellular injury. The direct toxic effects of the drug or its metabolites on hepatocytes are typically responsible for this hepatic pattern of injury, which causes oxidative stress, mitochondrial dysfunction, and disruption of cellular activities. Furthermore, several drugs can activate immune-mediated systems that cause inflammation and cell death. To prevent further liver damage and the development of chronic liver disease, DILI necessitates the rapid diagnosis and removal of the offending substance. It might range from asymptomatic elevations in liver enzymes to total liver failure.[34]

Acute Liver Failure

Acute liver failure (ALF) is defined as an abrupt decline in liver function that occurs within days to weeks in a patient without a history of liver disease. The primary cause of the hepatic pattern of injury in ALF is massive hepatocyte necrosis or apoptosis, which can occur due to a variety of etiologies such as viral hepatitis, drug toxicity (especially acetaminophen overdose), autoimmune hepatitis, or ischemia. Strong inflammatory reactions, mitochondrial dysfunction, and high oxidative stress all contribute to significant liver cell damage and decreased liver function.[35]

Table 1. Summary of Liver Enzymes and Liver Function Tests

Test	Origin/Source	Usage/Indication
AST/ALT	AST is present in the mitochondria and cytosol of hepatocytes; ALT is mainly found in the hepatocyte cytosol.	Evaluates hepatocellular injury. ALT is more liver-specific; elevated levels suggest damage to liver cells.
Bilirubin	A breakdown product of hemoglobin that is processed by the liver.	Assesses the liver's ability to excrete bilirubin; used to detect cholestasis, hemolysis, and disorders of bilirubin metabolism.
ALP	Primarily produced by bile duct epithelial cells (also found in bone and placenta).	Used to evaluate cholestatic liver disease; elevated levels often indicate bile duct obstruction or other cholestatic processes.
GGT	Produced by liver cells, especially those lining the bile ducts.	Helps confirm the hepatic origin of an elevated ALP; also used to assess alcohol-related liver injury.
5'-NT	Found predominantly in the cells lining the bile ducts.	Highly sensitive for cholestasis; used to assess bile duct obstruction and other cholestatic conditions.
LDH	Found in nearly all tissues, including the liver.	A non-specific marker of tissue damage; may be elevated in liver injury as well as other conditions affecting various tissues.
Albumin	Synthesized exclusively by hepatocytes.	Reflects the liver's synthetic function; low levels may indicate chronic liver disease, malnutrition, or other conditions affecting protein synthesis.
PT	Measures the production of clotting factors (e.g., II, VII, IX, and X) by the liver.	Evaluates liver synthetic function; a prolonged PT suggests impaired production of clotting factors due to liver dysfunction or vitamin K deficiency.

Since the liver is essential for metabolism, cleansing, and preserving hemostasis, acute liver failure carries serious and varied risks. Hepatic encephalopathy, coagulopathy, metabolic imbalances, and multi-organ failure are major consequences that, if left untreated, can be fatal. Since acetaminophen poisoning is the most frequent cause of ALF in the US and many other nations, it is important to pay close attention to this during diagnostic examinations. To improve outcomes, the underlying cause must be quickly identified and treated; in certain situations, a liver transplant may be necessary to preserve the patient's life.[35]

Other diseases

There are several other conditions that also follow a hepatocellular pattern. These include autoimmune hepatitis, ischemic hepatitis, and various genetic and metabolic disorders, each with distinct pathomechanisms leading to liver cell damage. Autoimmune hepatitis (AIH), a chronic inflammatory liver disease, causes the immune system to assault hepatocytes improperly. This immune-mediated damage, caused by autoreactive T cell activation and the production of autoantibodies against liver antigens, resulting in chronic inflammation and hepatocyte necrosis. The fibrosis generated by the ongoing immune response exacerbates the hepatic damage pattern. Ischemic hepatitis is another condition caused by an abrupt decrease in blood supply to the liver, which can occur as a result of respiratory failure, septic shock, or heart failure. When the liver's metabolic needs are not satisfied, necrosis occurs, especially in the centrilobular sections, causing severe hepatocellular damage.[36,37]

Hepatocyte buildup of harmful substances is another way that hereditary and metabolic disorders including hemochromatosis, Wilson's disease, and alpha-1 antitrypsin deficiency cause hepatocellular injury. Excessive copper accumulation in Wilson's disease leads to oxidative stress and cellular damage. Hemochromatosis is defined by iron excess, which results in reactive oxygen species and severe hepatocyte necrosis. Insufficient alpha-1 antitrypsin promotes abnormal protein buildup in the liver, resulting in fibrosis and inflammation. Each of these ailments demonstrates the various ways in which hepatocellular injury can occur, as well as the complexities of liver conditions that all follow the same pattern of cellular damage.[38]

DISEASES WITH CHOLESTATIC PATTERN

Primary Biliary Cirrhosis (PBC)

Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease characterized by the gradual loss of tiny intrahepatic bile ducts, resulting in decreased bile flow (cholestasis) and eventual liver damage. The pathophysiology of PBC is an inflammatory response in which T cells mistakenly assault the epithelial cells lining the bile ducts, resulting in chronic inflammation and fibrosis. This autoimmune response causes the bile ducts to become damaged and finally vanish, resulting in bile buildup within the liver. This cholestasis causes the retention of bile acids and other toxic chemicals, which further harms hepatocytes and promotes fibrosis. If not addressed, this progressive injury can lead to liver cirrhosis and liver failure.[39,40]

Primary Sclerosing Cholangitis (PSC)

Primary sclerosing cholangitis (PSC) is a chronic liver disease characterized by increased inflammation, fibrosis, and bile duct stricture. Chronic inflammatory processes cause fibrotic changes in the bile ducts,

restricting and finally obliterating them. This is the pathomechanism that drives PSC. This barrier limits bile flow, causing cholestasis and the accumulation of bile acids and other toxic substances in the liver. These accumulating substances cause cirrhosis and liver failure by repeatedly harming, inflaming, and fibrosing the hepatocytes. Although the exact origin of PSC is unknown, ulcerative colitis, in particular, is frequently associated with inflammatory bowel illnesses.[41]

Bile Duct Obstructions

The cholestatic pattern of liver injury is caused by bile duct obstruction, a condition that prevents bile from passing normally from the liver to the small intestine. Cholangitis and choledocholithiasis are the most common causes of bile duct obstruction. Choledocholithiasis is the presence of gallstones that obstruct bile flow in the common bile duct. This blockage causes bile acids and bilirubin to accumulate in the liver, damaging hepatocytes and leading in cholestasis. Retained bile components inflame the bile ducts and increase their pressure, causing severe injury to the liver cells.[42]

Cholangitis is a bile duct infection and inflammation that is commonly caused by choledocholithiasis. Gallstone obstructions can provide an ideal environment for the growth of bacteria, which can cause sickness. Bacteria migrate up the bile ducts from the small intestine, causing fever, jaundice, inflammation, and abdominal pain. This inflammatory process worsens cholestasis by increasing bile flow and pressure inside the bile ducts, resulting in further hepatocyte injury and fibrosis.[42]

Although cholangitis and choledocholithiasis are the most common causes of bile duct obstruction, it's important to note that other illnesses might exacerbate the situation. Tumors such as pancreatic cancer and cholangiocarcinoma can compress or invade the bile ducts, causing blockage. Parasite infections, such as liver flukes, can also obstruct the bile ducts by physically filling the lumen or causing an inflammatory reaction. These illnesses, albeit less common, can induce cholestatic liver disease by restricting bile flow and accumulating toxic bile components in the liver.[43,44]

Genetic Cholestatic Syndromes

A class of hereditary diseases known as genetic cholestatic syndromes cause problems with the production or flow of bile, which in turn causes a cholestatic pattern of liver damage. Alagille syndrome, benign recurrent intrahepatic cholestasis (BRIC), and progressive familial intrahepatic cholestasis (PFIC) are a few of these syndromes. The function of proteins involved in bile secretion is disrupted by mutations in genes such ATP8B1, ABCB11, and ABCB4 in PFIC. This accumulation of bile acids within hepatocytes results in cellular damage, inflammation, and fibrosis. Similar genetic abnormalities cause intermittent episodes of cholestasis in BRIC, a milder variation with less severe outcomes.[45]

Mutations in the JAG1 or NOTCH2 genes cause Alagille syndrome, which impairs bile duct development and eventually results in cholestasis due to bile duct scarcity. Hepatocyte damage, fibrosis, and the clinical signs of cholestasis—jaundice, pruritus, and fat malabsorption—are caused by the retention of bile acids and other bile components in the liver. These hereditary conditions emphasize the vital function of bile flow and secretion in preserving liver health as well as the dire repercussions that result from altering these functions.[46]

DISEASES WITH MIXED PATTERN

Because liver pathology is so complex, illnesses affecting the bile ducts or hepatocytes might progress to a mixed pattern of harm. Hepatocellular disorders are initially different in that they mainly affect the liver parenchyma, whereas cholestatic diseases affect the bile ducts and flow. On the other hand, when the disease advances, significant damage is caused, leading to a mixed pattern with cholestatic and hepatocellular characteristics. For example, hepatitis B and C, which are chronic viral hepatitis, start as hepatocellular damage, develop to cirrhosis and fibrosis, impede bile flow, and cause symptoms that are indicative of cholestatic disease. Similar to this, autoimmune hepatitis develops into a mixed pattern that damages the bile ducts through progressive inflammation. Furthermore, genetic/metabolic illnesses such as Wilson's disease and drug-induced liver injury can result in mixed injury, which combines immune-mediated bile duct destruction with direct hepatocyte toxicity.[1,2,31]

Furthermore, nonalcoholic steatohepatitis (NASH), a form of nonalcoholic fatty liver disease (NAFLD), is characterized by hepatic damage, including steatosis, ballooning degeneration, and inflammation. In advanced stages, NASH can progress to cirrhosis, which is defined by fibrosis that disrupts normal liver architecture and bile flow, resulting in combined hepatocellular and cholestatic damage. Similar effects can be found in alcoholic liver disease (ALD), which begins with hepatocellular damage caused by continuous alcohol consumption but can progress to cirrhosis and

cholestasis.[32,33]

On the other hand, cholestatic illnesses affecting the intrahepatic and extrahepatic bile ducts, respectively, such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), can cause substantial liver damage over time. For example, PBC first presents with cholestasis-related symptoms such increased ALP and gamma-glutamyl transferase (GGT), which are caused by immune-mediated small bile duct damage. Chronic cholestasis presents a mixed pattern of cholestatic and hepatocellular features as the disease progresses, causing periportal inflammation, hepatocyte damage, and ultimately cirrhosis. Similar to this, PSC causes bile duct inflammation and fibrosis, which results in cholestasis and biliary cirrhosis. This may eventually lead to hepatocyte necrosis, severe liver damage, and signs of hepatocellular injury.[40,41]

These examples illustrate how liver diseases, whether initially hepatocellular or cholestatic, can converge into a mixed pattern of injury as they progress, highlighting the complexity of liver disease pathogenesis. The transformation from a specific pattern to a mixed pattern underscores the need for comprehensive diagnostic and therapeutic approaches to manage advanced liver diseases effectively.

CONCLUSION

In this review article, we have provided a comprehensive examination of the various patterns of liver injury, emphasizing the differences between hepatocellular and cholestatic patterns and their respective diagnostic approaches. By exploring the pathophysiological mechanisms, clinical presentations, and diagnostic tests associated with these patterns, we aim to enhance the understanding of liver diseases among clinicians and researchers. Our detailed discussion included the critical roles of liver enzymes and function tests, which are indispensable tools in diagnosing and managing liver diseases. Moreover, we delved into a wide range of liver conditions characterized by hepatocellular and cholestatic patterns, highlighting the importance of accurate diagnosis and tailored management strategies. Through this thorough exploration, we underscore the complexity of liver diseases and the necessity of a nuanced approach to diagnosis and treatment. It is our hope that this review will serve as a valuable resource for future studies and educational purposes, providing a solid foundation for medical students, researchers, and clinicians. By fostering a deeper understanding of liver pathologies, this review aims to contribute to the ongoing advancements in hepatology, ultimately improving patient care through more effective diagnostic and therapeutic approaches.

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