

Approach to the patient with abnormal liver biochemistry

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Abstract

Altered liver function tests are a common finding that requires careful interpretation and thorough correlation with the patient's clinical picture. This paper provides a systematic and practical approach to the management of patients with alterations in their liver biochemistry. The fundamental concepts of liver anatomy and physiology are reviewed, emphasizing the importance of understanding the microscopic organization of the organ and key metabolic processes. The most used liver tests, their interpretation and the patterns of alterations that may occur will be described, and the importance of a detailed anamnesis will be emphasized.

Guidelines are provided for the diagnostic approach according to the pattern of alteration observed and the different patterns of transaminase elevation, from mild to moderate and severe, and their possible causes are discussed in detail. The importance of considering fatty liver disease as a frequent cause of mild and persistent transaminase elevations is highlighted, and noninvasive tools for the evaluation of liver fibrosis, such as specialized scores and markers, are mentioned.

In summary, this document presents an updated and practical text for the proper interpretation of alterations in liver biochemistry, emphasizing the importance of a close correlation with the clinical context of the patient, which will allow an accurate diagnosis and appropriate management.

Keywords: Liver Function Tests; Diagnostic Techniques; Digestive System; Liver biochemistry

1. Introduction

Liver profile alterations are one of the most frequently observed abnormalities, both in patients seen in the hospital setting and in primary care consultations. In the latter group they even constitute up to 10% of casual findings in routine tests of alterations in the profile of patients presenting with nonspecific or even asymptomatic symptoms.

Within the interpretation of the abnormality in liver biochemistry we can discern its origin, severity, chronicity and with the good clinical context of our patients we can establish an adequate diagnosis or false positives. In this way we can benefit with an adequate and opportune management of the patients, understanding from the structural and functional hepatic part to the reason why they are affected according to different etiologies, in order to understand the different interpretations that will be given regarding the anomalies present in the hepatic biochemistry tests. (1)

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2. Methodology

A systematic review was conducted by selecting original articles, available research reviews, written in English and/or Spanish, through recognized databases such as Wiley, PubMed, Scielo, ScienceDirect, PLOS ONE, among others. Regardless of the publication year, the search terms used included Abnormal Liver Chemistries, abnormal liver function tests, hepatocellular pattern, cholestatic pattern.

3. Results

3.1. Basic anatomy and physiology

3.1.1. Macro anatomy

The liver is one of the largest organs of the human being, and also one of the most important. It is responsible for most of the metabolic functions, among others concerning carbohydrates, lipids, proteins and external substances (e.g. drugs, herbals, toxins, etc.).

It can be divided anatomically into parenchyma, properly speaking, and biliary structure, the latter formed by common hepatic ducts that when joined together form the common hepatic duct that together with the cystic duct form the common bile duct, which ends in the second portion of the duodenum in the ampulla of Vater.

The irrigation is particular and differs from the typical irrigation of other organs, since 80% of the hepatic circulation is of venous origin, through the portal vein, which is formed by the union of the superior mesenteric vein and the splenic vein. The arterial irrigation is given by the hepatic artery, branch of the celiac trunk, responsible for 20% of the hepatic irrigation. It must be considered that the venous irrigation has a greater relationship with the hepatocytes, while the arterial irrigation supplies nutrients especially to the biliary tract.

The venous drainage is provided by the three suprahepatic veins that leave the liver and form the inferior vena cava before entering the right atrium.

3.1.2. Micro anatomy

To understand the functional unit there are 2 types of descriptions (figure 1): a classic one (hexagonal lobule that is formed by portal triads and in the center a centrolobulillar vein) and another one in relation to the hepatic acinus (provides greater physiological correlation), and that has by structure the portal triad in the center, the centrolobulillar veins towards the ends and makes that we can distinguish microscopically in the liver 3 zones:

- Zone 1: the one closest to the portal zone.
- Zone 2: intermediate zone.
- Zone 3: the zone around the centrolobulillar vein.

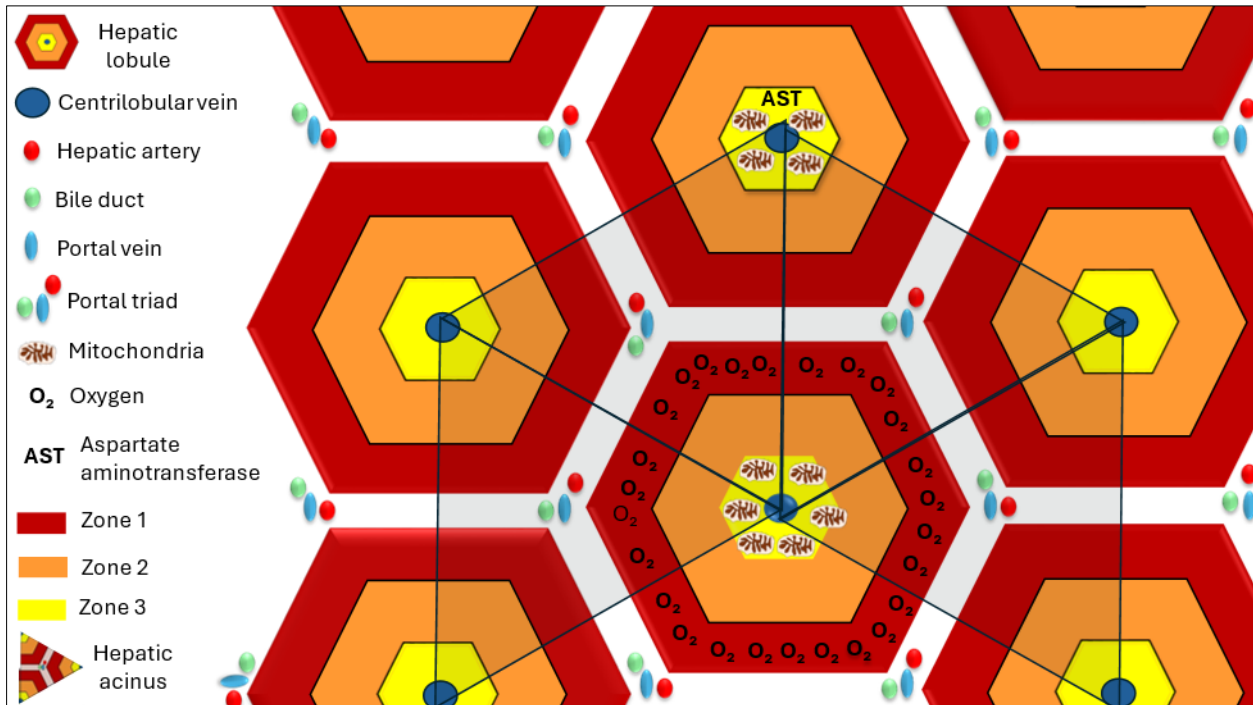


Figure 1 Microscopic anatomy and hepatic zones. Own elaboration.

In this microscopic organization, the first row of hepatocytes after the portal triad are specialized hepatocytes called oval cells capable of differentiating when the liver undergoes noxas in the regeneration process and become cells of the hepatic parenchyma or of the biliary tract, according to the needs of the organ. Between the portal triad and the centrilobular vein there are rows of hepatocytes that are surrounded by hepatic sinusoids, specialized vascular structures, characteristically with a single row of endothelial cells, without intercellular junctions, abundant fenestrations and without basement membrane. Between the rows of hepatocytes and the sinusoids there is a virtual space or Disse's space where Kupffer cells are found, which are part of the reticuloendothelial system (they act as the most important defense cells of the liver) and stellate cells, which in the quiescent state participate in the storage of lipids and vitamin A, but when the liver is subjected to a noxa, they are cells that are activated and can transform into fibroblasts, thus becoming the cells responsible for the deposition of the collagen matrix in the patient who progresses to cirrhosis.

In general terms, the substances enter the liver through the portal triad in venous blood, which configures an oxygen and nutrient gradient that is important to understand many of the pathological alterations. In this gradient, zone 1 (previously described) has a better energy supply and zone 3 has a greater shortage, due to a lower concentration of oxygen and nutrients. However, zone 3 is the most metabolically active zone, which is why it harbors the greatest number of mitochondria and is considered the most functional region of the liver. Contrary to the direction of blood flow, the flow of bile occurs, which is formed by the union of hepatocytes creating a canalicular lumen. The hepatocytes have a basolateral membrane (in contact with the blood circulation - the sinusoids) and a canalicular membrane (responsible for the formation of the biliary tree).

3.2. Metabolism

3.2.1. Bilirubin

The senescent red blood cells and in some situations hemolysis, generate release of hemoglobin, which enters the endothelial reticulum system for metabolism of the heme group, and this, through heme oxygenase will be converted to biliverdin, in turn reduced by bilirubin reductase and generating indirect or unconjugated bilirubin. This substance will travel through the blood circulation, transported by albumin to the hepatic sinusoids, where upon contact with the basolateral membranes of the hepatocytes it will be released from albumin and enter the hepatocyte through the organic anion transporter, undergoing in the endoplasmic reticulum its conjugation process by the enzyme Uridine-diphosphate Glucuronosyl Transferase (UGT), generating direct or conjugated bilirubin, which later passes to the light of the biliary tract through the specific transporter Multidrug Resistance Protein 2 (MRP2), route by which it is finally excreted. (2,3)

3.2.2. *Bile acids*

Bile acids originate in the metabolism of cholesterol, they can be of primary, secondary type (they originate from the hepatic metabolism itself), and other tertiary generated by the metabolism of the bacteria in the intestine, beginning later the process of enterohepatic circulation. (2,3)

3.3. **Hepatic tests**

The so-called hepatic tests are easily accessible studies, which should always be interpreted in the light of the pathophysiology in correlation with the clinical picture of the patient, who is the one that always gives meaning to all the medical action. These are important because they allow early differentiation of the different patterns of alteration with a view to the diagnostic approach. Any result that is outside the standard reference values will be considered an alteration of the liver tests (4).

These tests are of several types:

3.3.1. *Hepatocyte Integrity*

The so-called transaminases are enzymes present in hepatocytes released into the bloodstream in response to injury or cell death. The range of normality varies according to gender: for men the normal ALT values will range from 29 to 33 IU/L, and for women the range is between 19 and 25 IU/L. Values above these reference ranges should always be judiciously evaluated (3).

ALT - alanine aminotransferase (TGP): This is the most liver-specific enzyme, however, it is known to be expressed in striated muscle as well.

AST - aspartate aminotransferase (GOT): It is a less specific enzyme because it is also abundantly found in muscle tissues: skeletal, smooth muscle and cardiac muscle, which may be elevated in cases of myocardial infarction or myositis.

It should be noted that ALT is considered a more specific indicator of hepatic disease; AST concentration is more sensitive in cases of alcohol-related hepatic injury and some cases of autoimmune hepatitis as will be seen later.(1,3,5).

3.3.2. *Cholestasis*

Alkaline phosphatase - ALP: It is produced mainly in the liver, (particularly by the biliary epithelium) but it is also produced in bone, placenta, intestine, kidneys and leukocytes.

Considering this, pathological increases may occur in bone diseases (e.g. bone metastases, fractures) and cholestatic diseases such as choledocholithiasis, primary biliary cholangitis, primary sclerosing cholangitis, intrahepatic duct obstruction and drug-induced cholestasis. In addition, hepatic congestion secondary to right heart failure can lead to cholestasis. While there are no data on the most likely causes of isolated elevated ALP in an asymptomatic population, vitamin D deficiency is likely to be the most common cause. Whereas, in the case of suspected systemic disease, isolated elevations of alkaline phosphatase have been associated with hepatic amyloidosis.(6)

Gamma glutamyl transpeptidase - GGT: Its clinical value is generally linked to alkaline phosphatase levels, specifically to determine the hepatic origin of alkaline phosphatase. However, it is a highly nonspecific enzyme that can be induced, among other things, by fatty deposits in the liver and alcohol use. It can be found in the kidney, intestine, prostate and pancreas, but not in bone. Isolated GGT is most commonly elevated as a result of obesity, excessive alcohol consumption or drug induced.

Bilirubin: Its elevations may be an expression of hepatic or extrahepatic disease. Its elevations can occur at the expense of the indirect fraction, which is usually explained by hemolysis or alteration of the conjugation, and direct which generally corresponds to a hepatic disease or obstruction of the biliary tract (3-5,7,8).

3.4. **Function of the hepatic mass**

Serum albumin: It assesses the liver's synthesis capacity because it is only produced in this organ and has multiple biological functions (oncotic pressure, substance binding, etc). However, albumin concentrations are not only reduced due to decreased synthesis but are also associated with other clinical situations such as sepsis, systemic inflammatory response, nephrotic syndrome, malabsorptive disorders, gastrointestinal losses, or dietary restrictions.

Prothrombin time (PT) and INR: Seeks to measure the synthetic capacity of the liver in relation to the production of coagulation factors (II, V, VII, IX and X). When the liver suffers a hepatic injury with loss of >70% of the synthetic function, this will result in a reduction in the production of coagulation factors, which is expressed in the prolongation of the PT or INR.(8)

3.5. Evaluation of hepatic fibrosis

Clinical and laboratory parameters: Different scores have emerged in recent years in order to evaluate noninvasively the degree of liver fibrosis, among them we have the AST/ALT ratio, APRI, NFS, BARD Score and FIB-4, the latter is the most used in our environment and has presented higher performance with a sensitivity of 65% and a specificity of up to 97%. However, all the previous scores have not been reproducible, and each one has limitations (12).

Specialized markers: They are hardly used in our daily practice, but they are useful because they all participate in the process of hepatic fibrosis, so far they have not been tested and the results cannot be analyzed in isolation and without the clinical context of the patient, so panels have been created for the realization, among them we find: serum levels of hyaluronic acid, PIIINP, Pro-C3 and laminin. (12)

3.6. Platelets: What is their role in liver disease?

A reduction in platelet count, called thrombocytopenia, is one of the most frequent hematologic abnormalities in patients with chronic liver disease and is an indicator of advanced disease. Multiple factors can explain it: reduced production, splenic sequestration, and increased destruction.

The decrease in production is a consequence of bone marrow suppression and can also be caused by excessive alcohol consumption, iron overload, drugs and viruses, or in other cases by decreased thrombopoietin levels secondary to hepatic injury. Hypersplenism is generally a consequence of portal hypertension seen in advanced hepatic fibrosis; and with respect to platelet destruction, it is also non-specifically increased in liver cirrhosis by increased shear stress forces, fibrinolysis and bacterial translocation, while in specific causes hepatic autoimmune disease may be found, where immunological destruction of platelets mediated by antiplatelet immunoglobulin usually occurs. (4)

3.7. Diagnostic generalities

3.7.1. When to order liver tests?

When considering the performance of liver tests, we must take into account that the alteration can be completely asymptomatic or with non-specific symptoms, so it should be considered to include the hepatic biochemical profile within the study and follow-up of the patients in a routine way to improve the opportunity in the diagnosis of some entities.

An additional scenario to consider is the patient at high risk of developing liver disease such as those with a history of pre-existing autoimmune diseases, inflammatory bowel disease, primary biliary cholangitis or primary sclerosing cholangitis. In addition, toxicity screening should always be performed in those patients using hepatotoxic drugs such as macrolides, nitrofurantoin, carbamazepine, methotrexate, antituberculosis drugs, etc. (5).

- Interrogation and correlation with the clinical context.
- When interpreting any alteration in liver tests, the following situations or conditions should always be inquired (Figure 2):
- Alcohol consumption: duration, frequency, type, amount.
- Usual residence and recent travel: particular attention to tropical regions.
- Use of intravenous drugs or blood transfusions.
- Sexual habits: promiscuity, risky sexual behavior.
- Recent use of conventional drugs.
- Use of natural products or substances (herbs, roots, drops, multivitamin supplements, hyper protein solutions, etc.).
- Tattooing, piercing users.
- Occupational exposures.
- Family history of cirrhosis, Wilson's disease or hemochromatosis.

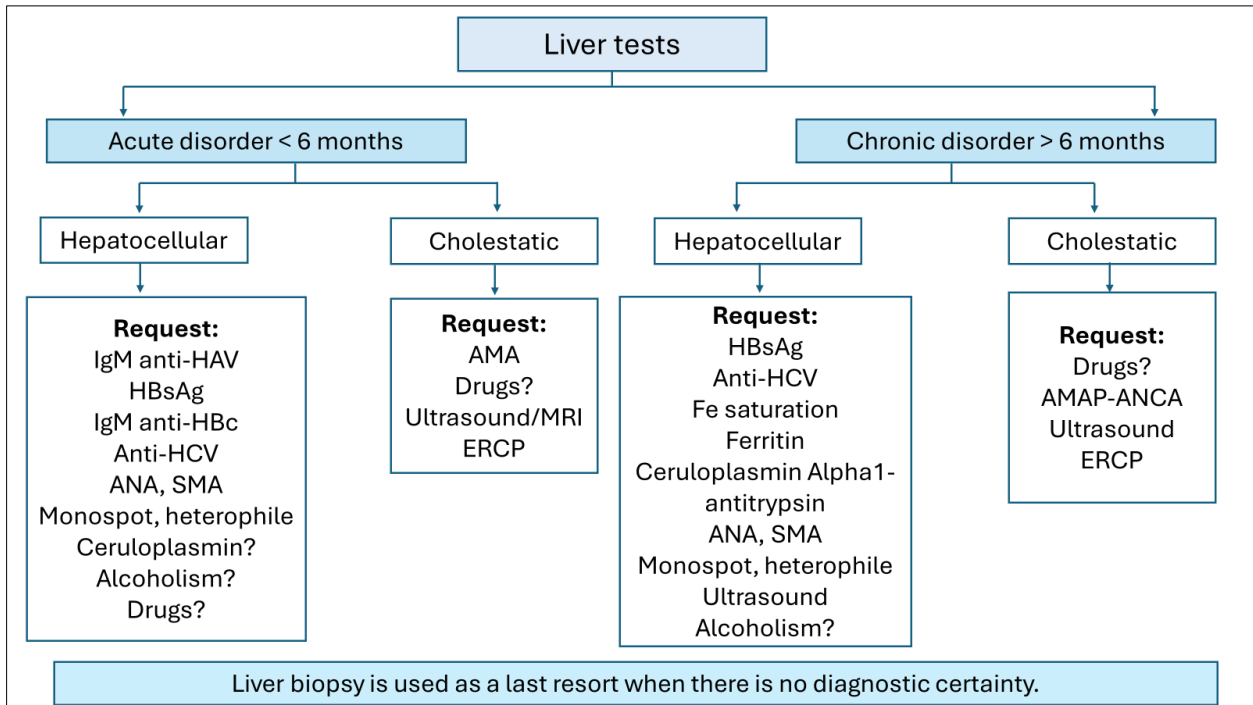


Figure 2 Diagnostic algorithm according to chronicity and type of pattern. Modified from: Jameson, J. Fauci, A. Kasper, D. Hauser, S. Harrison. Principle of Internal Medicine. 20e. McGraw-Hill Education. All rights reserved.

Additionally, the approach recommends asking 3 fundamental questions for the diagnostic approach:

- How?

Assess the pattern of alteration (hepatocellular, cholestatic or mixed as explained below), the magnitude (mild, moderate or severe), its nature, the rate of alteration (increase or decrease), etc.

- Who?

Patient characteristics such as race, weight, ethnicity, age, food - drug - herbal habits, symptoms, etc.; outpatient or inpatient. Always assess considering local epidemiology.

- When?

Time at which the alteration of the tests appears, its relationship with age, temporal correlation with substance intake or comorbidities (3,5,7,9,10).

4. Patterns of alteration of liver tests (Figure 3)

4.1. Hepatocellular pattern

It is determined by an affection of transaminases, enzymes that make transmission of amino or keto groups between aspartic acid or oxaloacetic acid (AST/TGO) or between alanine acid and pyruvic acid (ALT/TGP). Both types require pyridoxal phosphate (vitamin B6) for their synthesis, but the most dependent is ALT, and this has an important clinical value because in malnourished or alcoholic patients with nutritional deficiencies, including vitamin B6, the transaminase alteration profile will have a predominance of AST over ALT (AST/ALT ratio >2).

In the hepatocellular pattern, the main characteristic is the disproportionate increase of ALT and AST in contrast to FA and GGT, due to the release of aminotransferases from hepatocytes. For this reason a score has been created to help determine the pattern of the lesion, the R-value, which is calculated as follows: $(ALT \div LSN \text{ of ALT}) / (FA \div LSN \text{ of FA})$. (13)

The upper limit for ALT was already described above according to sex and for the alkaline phosphatase value the laboratory value is proposed. An R value > 5 suggests a hepatocellular pattern, > 2 to < 5 suggests a mixed pattern, and < 2 suggests a cholestatic pattern.(13)

Hepatocellular disease	Cholestatic disease
Non-alcoholic steatohepatitis	Primary biliary colangitis
Fatty Liver Associated with Metabolic Dysfunction (MALFD)	Primary sclerosing colangitis
Chronic viral hepatitis	Malignant bile duct obstruction
Alcoholic liver disease	Benign biliary tract obstruction
Toxic-drug hepatitis	Drug-toxic hepatitis
Autoimmune hepatitis	Autoimmune colangitis
Hemochromatosis	Sarcoidosis
Wilson's disease	
Alpha-1-tryptsin deficiency	

Figure 3 Diseases associated with pattern types. Modified from: Fuente Orlando, W., & Ferrera, G. (2013). How to approach the rise of liver enzymes in healthy people? The importance for the general practitioner. In Rev Gastroenterol Peru (Vol. 33, Issue 3).

It has already been mentioned that AST is more nonspecific, besides having an 80% mitochondrial localization (this is how in mitochondrial lesions, for example, in those of hypoxic-ischemic type in hepatocytes, there is a greater predominance of AST), while ALT has a 100% cytoplasmic predominance.

Within the common patterns there are some authors who divide the causes according to the number of times that transaminases are elevated with respect to the Upper Reference Limit - ULR, defining according to the magnitude of the elevation in mild if AST and ALT increase between 2 to 5 times the normal upper limit, in which case an exhaustive diagnostic study should not be performed and instead it can be considered to do follow-up and control in 3 months, and if the elevation persists to initiate an intensive diagnostic effort; elevation will be moderate if the increase is between 5 to 15 times the RSL and severe if the elevation is greater than 15 times the RSL. (3,8)

4.1.1. Severe elevations of transaminases

Hypoxic-ischemic hepatitis

These are usually patients who have been critically ill, with states of hypotension, hemodynamic shock, hypoperfusion, and particularly compromising liver irrigation. It can also be seen in patients with outflow obstruction (e.g. Bud-Chiari syndrome or right heart failure, constrictive pericarditis, acute vena cava obstructions). They are usually massive elevations of transaminases (>10,000 IU), without very significant elevations of bilirubin, and that as relevant clinical data have a rapid improvement after removing the noxa. They are predominant damage of zone 3 of the hepatic acinus, where as mentioned there is a great abundance of mitochondria, reason for which there is a greater predominance of AST over ALT. The ALT/LDH ratio may help in its differentiation, which will be < 1. It is more frequently found in comorbid patients (1,9).

Toxic lesion: In general toxicity is a diagnosis of exclusion, and as in any case of hepatic involvement, a good interrogation should be done trying to look for exposure to the agent. Its pattern of presentation may be like hypoxic ischemia due to the fact that once the exposure to the substance is over, the patient improves, although more slowly. (1,11)

4.1.2. Moderate to severe elevations of transaminases

*Viral hepatitis: may have transaminase elevations between 5 and 10 times the RSL, but on rare occasions elevations >10 times the RSL may be found, they are usually accompanied by concomitant elevations of bilirubin between 5 - 10

times the RSL. In acute cases, the clinical presentation is nonspecific, given by asthenia, adynamia, nausea, hyporexia, abdominal pain, vomiting, jaundice, and the pattern of transaminase decline is slow.

In cases of chronic hepatitis, there may be periods with normal liver enzyme values, as occurs in some patients with cirrhosis, without this being related to the severity or persistence of the disease that the patient may present.

4.1.3. Moderate elevations of transaminases

Acute biliary obstruction: These are patients who are typically admitted to the emergency department for abdominal pain, nausea, vomiting and liver biochemical profile compatible with hepatitis, with elevated transaminases, predominantly AST and in whom acute bile duct obstruction is documented, in most cases due to bile duct stones that obstruct the flow of bile increasing the pressure in the biliary tract causing collapse of the vascular structures of the portal triad and that is why the paraclinical expression can simulate a hypoxic-ischemic hepatitis. Once the obstruction is resolved, the tests quickly normalize. Bilirubin elevation is usually significant, generally at the expense of the direct fraction, its value is usually 5-10 times above the RSL or even >10.

Alcoholic hepatitis: It is caused by excessive alcohol consumption, and concomitant bilirubin elevation may be found. The AST/ALT ratio is >2 (this is explained by the fact that pyridoxal phosphate - vitamin B6 is required, which in this case is usually deficient, and which prevents the synthesis of ALT to a greater extent than AST) (1).

4.1.4. Mild elevation of transaminases

First, extrahepatic causes should be excluded since not infrequently, particularly in patients without risk factors for alteration of liver tests, a frequent muscular origin can be found, for example, in healthy patients who are athletes, bodybuilders, etc. In fact, for many authors, the recommendation is to repeat the liver profile to assess the persistence of the elevation.

The second thing to do is to inquire about the consumption habits and the presence of toxic substances, in which case the tests should be suspended and repeated, and in case of persistent alterations, to verify the real suspension of toxic substances and to advance in the diagnostic effort.

The recommendation is to always screen for viral hepatitis (hepatitis B surface antigen and antibodies against hepatitis C), especially in young or sexually active patients. Study Wilson's disease or hemochromatosis in areas endemic for genetic diseases, when consanguinity between parents is documented, or family history of liver, neurological or psychiatric diseases.

In middle-aged women with a history of autoimmune diseases (primary hypothyroidism, type 1 diabetes mellitus, vitamin B12 deficiency, etc.), the presence of autoimmune hepatitis should be studied.

If after this screening no obvious cause is found to explain the mild and persistent elevation of transaminases, fatty liver should be investigated, which should be studied in principle with liver ultrasound and sometimes it will be important to request transient liver elastography. It must be taken into account that fatty liver is an increasingly frequent condition in the world and that on many occasions it will require confirmation and staging with liver biopsy (9,10).

4.2. Cholestatic pattern

Its defining and essential factor is the elevation of alkaline phosphatase - ALP of biliary origin, therefore, bilirubin elevation is not necessary to define a cholestatic pattern, although they are frequently elevated concomitantly.

AF is responsible for catalyzing the hydrolysis of organic phosphates at alkaline pH in cell membranes, mainly in the canalicular lumen of hepatocytes and cholangiocytes, and is considered to have a half-life of 7 days. It increases by regurgitation, excretion or induction and as mentioned it is not specific to the liver.

As a second enzyme we find GGT - Gamma glutamyl transpeptidase, whose only usefulness in these cases is the confirmation of the hepatobiliary origin of the elevated AF, on its own it is highly non-specific. This is a microsomal enzyme potentially inducible by drugs, alcohol or steatosis. It is useful, among other things, for the classification of familial cholestasis, where there is a specific congenital problem in the 3 transporters involved in bilirubin synthesis.

Once AF elevation is found and its biliary origin is confirmed with concomitant GGT elevation, in addition to the clinical history and physical examination, its origin should be confirmed with concomitant GGT elevation and if so, an imaging study should be requested in the first instance (hepatobiliary ultrasound of choice) to assess the presence of a biliary obstruction causing cholestasis. If there is a report of intra or extrahepatic biliary tract dilatation, there is most probably an obstructive process; however, when it is not described, there is a 50% probability that there is undetected obstruction, in which case a cholangioresonance - cholangioMRI or a biliopancreatic endosonography should be performed, both with adequate sensitivity and specificity for the diagnosis of biliary tract stones or obstructive lesions.

If no mechanical or obstructive lesion is detected by imaging, other non-obstructive diseases such as primary biliary cholangitis (more frequent in middle-aged women, with elevated AF, diagnostic imaging without dilatation or obstruction, positive antimitochondrial antibodies [AMA+], increased immunoglobulin M) should be considered, primary sclerosing cholangitis (more frequent in men, comorbidity with inflammatory bowel disease, particularly ulcerative colitis, with data in cholangioRM or endoscopic retrograde cholangiopancreatography - ERCP of areas with stenosis and dilatation of the biliary tract, positive anti-cytoplasmic neutrophil antibodies - ANCA+).

In other cases, we can speak of infiltrative lesions of the hepatic parenchyma in hepatic or extrahepatic diseases such as lymphomas, tuberculosis, or metastatic lesions; not forgetting hepatic amyloidosis that can present with cholestatic pattern. In these cases the clinical manifestations will depend to a great extent on the primary disease.

As in the case of elevated transaminases, in case the diagnostic impression of the cholestatic pattern is guided by the consumption of toxic or exogenous substances, these should be suspended and the tests repeated, which in case of normalization would support the diagnosis of cholestatic reaction due to drugs.

If after all this diagnostic approach is not possible to determine the cause, in many cases a hepatic biopsy should be performed (2,3,5,10).

4.2.1. Hyperbilirubinemia

Indirect (unconjugated) hyperbilirubinemia: the presence of a hemolytic process should be assessed, especially if there is concomitant anemia, also think about ineffective erythropoiesis, reabsorption of hematoma, and know that the most frequent cause of isolated indirect hyperbilirubinemia is Gilbert's syndrome, a congenital disorder of metabolism and that leads to a reduction of the enzymatic activity of UGT, responsible for bilirubin conjugation. (Figure 4).

Unconjugated or indirect hyperbilirubinemia	Conjugated or direct hyperbilirubinemia	Mixed hyperbilirubinemia
Increased production: <ul style="list-style-type: none"> • Hemolysis • Ineffective erythropoiesis 	Without cholestasis: <ul style="list-style-type: none"> • Dubin Johnson disease • Rotor disease 	Alteration of hepatocellular function: <ul style="list-style-type: none"> • Acute or subacute hepatocellular damage. • Chronic hepatocellular disease.
Alteration in conjugation: <ul style="list-style-type: none"> • Gilbert's disease • Crigler-Najjar disease 	<ul style="list-style-type: none"> • Intrahepatic colestasis • Extrahepatic cholestasis 	

Figure 4 Diseases associated with hyperbilirubinemia. Source: Caballería, L., & Parés, A. (2003). Daily consultation. What would you do when faced with... an icteric patient Differential diagnosis. In 70 Med Integral (Vol. 41, Issue 2).

Direct (conjugated) hyperbilirubinemia: the alteration occurs after conjugation, either in the specific transporter as in the case of MRP2 gene mutation in Dubin-Johnson syndrome or in other genetic alterations such as Rotor syndrome.

In more frequent conditions we will find obstruction of the biliary ducts, viral hepatitis, cirrhosis of any origin, cholestatic autoimmune diseases, total parenteral nutrition, drugs, evanescent duct lesions due to toxicity or autoimmunity (1,4) (1,4).

5. Conclusions

The cholestatic pattern is defined by the predominant increase of alkaline phosphatase - ALP, not bilirubins.

- To confirm the hepatic origin of ALP, GGT should be requested.
- ALT is the most specific of hepatic involvement.
- In liver disease due to alcohol abuse, an AST/ALT ratio >2 will be found, which is explained by vitamin B6 deficiency that decreases ALT production.
- Hypoxic-ischemic liver injury causes hepatocellular pattern involvement, and characteristically there is a rapid fall in transaminases after correction of the disorder. In this condition the AST/ALT ratio is usually >1 because in ischemia zone 3 of the hepatic acinus, which has many mitochondria and harbors 80% of AST, suffers most.
- The most frequent cause of isolated indirect hyperbilirubinemia is Gilbert's syndrome.
- Fatty liver should always be considered when mild and persistent elevation of transaminases is found, particularly in overweight or obese patients.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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