Ischemic Hepatitis – Intercorrelated Pathology

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ABSTRACT

Ischemic hepatitis is an important, yet underdiagnosed pathological condition seen in either cardiology or hepatology clinics or intensive care units. The main causes are severe heart failure, circulatory and septic shock. Close monitoring of biological tests (AST, ALT, LDH) together with hemodynamic parameters (blood pressure, cardiac output and central venous pressure) allow for rapid and accurate diagnosis. Correction of hemodynamic parameters, hypoxemia, hepatic and/or renal dysfunction leads to a more favorable outcome of these patients.

Keywords: ischemic hepatitis, severe heart failure, shock, biological tests, hemodynamic parameters.

INTRODUCTION

Ischemic hepatitis (IH) is a clinical, biological and histological syndrome characterized by a rapid, significant and transient rise in the plasma aminotransferase level (AST, aspartate aminotransferase and ALT, alanine aminotransferase) in various pathological conditions, such as heart failure (HF), circulatory or septic shock, respiratory failure. The pathologic hallmark of IH is hepatocellular necrosis in the centrilobular zone, known as hepatic centrilobular necrosis(1). Ischemic hepatitis has also been referred to in the literature as “hypoxic hepatitis” (HH) or “shock liver”. The term “hypoxic hepatis”

emphasizes multifactorial pathophysiologic factors resulting in hypoxia and subsequent biological and histological changes. The term “shock” might not be very accurate, as centrilobular ischemia and necrosis are not always associated with shock.

Congestive hepatopathy describes a spectrum of clinical and biological manifestations (e.g., mild increase in plasma aminotransferase level) due to passive and often prolonged hepatic congestion occurring in the setting of right-sided heart failure (e.g., dilated cardiomyopathy, mitral stenosis, constrictive pericarditis). The morphological pattern is centrilobular congestion (1, 2). Conges-

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tive hepatopathy may precede the onset of ischemic hepatitis. However, there is a significant overlap between these two conditions. In fact, both ischemic and congestive hepatitis are the result of constant interaction and relation between cardiac and liver disease, related to specific pathophysiologic setting and different stages of heart failure.

Ischemic hepatitis is a pathological condition which is managed nowadays by at least three types of medical specialties: cardiology, hepatology and intensive care. There are still unmet needs concerning a relatively high incidence, underdiagnosis and poor prognosis of IH/HH, which require a more rigorous and extensive research in this field.

Three criteria are currently accepted for the diagnosis of IH/HH (3, 4):

- clinical setting, such as heart failure, circulatory or respiratory failure;
- sudden, significant, but transient raise in plasma aminotransferase level;
- exclusion of other causes of hepatic cellular necrosis, especially viral hepatitis or drug-induced hepatopathy.

Epidemiology and etiology

The concept of IH/HH has been initially described in the setting of HF, following the morphological changes induced by the passive liver congestion. Later, IH/HH would become increasingly recognized in critically ill patients admitted in intensive care units (ICU). A minimum 10 times sudden increase in plasma aminotransferase levels is the “cut-off” point for IH/HH diagnosis (5).

Incidence of IH has been previously reported between 0.6-1.5% amongst medical ICU patients (6). A more recent meta-analysis of 1782 patients concluded that IH/HH was diagnosed in 2.5% of subjects (7). The occurrence of IH was even higher (11%) in a multicentric study that enrolled 1066 patients during their ICU admission period (8). Moreover, 18% of patients with cardiogenic shock following an acute myocardial infarction had an aminotransferase level >20 times the upper limit of normal, as reported in a recent study (9).

There is a wide variation in IH/HH incidence, especially in critically ill patients, related to the underlying pathological condition of each patient

FIGURE 1. Multifactorial etiology of ischemic/hypoxic hepatitis – adapted from Waseem *et al* (4). HF=heart failure

and also to different cut-off values for the plasma aminotransferase level. For example, IH/HH was diagnosed in 1.46% cases amongst 33654 patients admitted to ICU, when IH/HH was defined as a rapid increase of AST/ALT ≥ 800 UI/L, excluding other causes (10).

The etiology of IH/HH is often multifactorial, with more than one risk factor identified as important triggers (Figure 1). Heart failure is the main etiopathogenic condition for IH/HH. In the previous meta-analysis (7), acute HF was present in 78% of patients with IH/HH. The risk of IH/HH was particularly high in the group of patients with right-sided HF and liver congestion, as a precondition for IH/HH (6).

Other risk factors for IH/HH, besides HF, are septic shock (approximately 23%), respiratory failure (approximately 15%), major cardiovascular surgery, anemia, hypovolemic shock, extensive burns, prolonged hypotension (4).

Preexistent hepatic injuries that may favor IH/HH occurrence has to be considered in some patients: chronic viral hepatitis, non-alcoholic hepatitis, hepatic disease with portal hypertension or toxic hepatitis (drug-induced). These conditions may raise important and difficult IH/HH diagnosis concerns.

Pathophysiology

The pathophysiologic mechanisms involved in hepatocyte necrosis in the setting of ischemic hepatitis are directly related to hepatic blood flow characteristics. Hepatic blood flow accounts for about 25% of the cardiac output, delivered to the liver via two vascular systems: the portal vein

system (approximately two thirds of the blood flow) and the arterial hepatic system (approximately one third). The portal blood is rich in nutritive elements but low in oxygen, whereas the arterial blood is rich in oxygen and accounts for more than 50% of the oxygen delivered in the liver. Thus, the liver is well protected against ischemia, primarily due to this dual system. Zones 1 and 2 (central zones) belonging to the liver acinar structure receive the highest amount of oxygen, while lower oxygen concentration blood is delivered to zone 3 (perivascular zone), which becomes the most vulnerable area when exposed to changes in the hepatic blood flow. Maximum oxygen extraction occurs in the liver (approximately 90%) (4).

Hepatic arterial blood flow and portal blood flow are interdependent. Reduced venous portal flow (e.g., in heart failure) leads to hepatic arterial vasodilation and increased flow, and vice versa, increased venous portal flow leads to reduced arterial blood flow. This autoregulation mechanism is adenosine mediated and is also known as “hepatic arterial buffer response” (11). Adenosine, which is synthesized by liver cells and Kupffer cells, is found around terminal hepatic arteries and is washed by the portal blood. A decrease in the portal blood flow leads to a rise in adenosine level and hepatic arteriolar dilation (11), whereas an increase in the portal blood flow leads to a decrease in the adenosine level in the space of

Mall, followed by arteriolar vasoconstriction and lower hepatic arterial flow.

Despite this autoregulation mechanism, most of the hepatic circulation via the portal vein system is not autoregulated, but depends on the mesenteric circulation and gradient between portal and hepatic veins pressure. A decrease in this gradient increases the ischemic risk of the liver (4).

Cellular hypoxia plays a central role in the pathophysiology of hepatic centrilobular necrosis typical for ischemic hepatitis (Figure 2). Three main pathological conditions are defined: 1) reduced hepatic flow and consecutive ischemia; 2) passive liver congestion; and 3) severe systemic hypoxia. These conditions are seen in heart failure (chronic, acute), shock and severe respiratory failure. In critically ill patients, all the above situations may be present in different combinations.

Heart failure is the major pathological condition that leads to IH/HH in approximately two thirds of cases. Heart failure with passive liver congestion is associated with an increased risk of IH/HH development. Passive hepatic congestion, usually chronic, is a major factor linked with IH/HH and probably a mandatory condition (5).

In congestive hepatopathy, structural changes developed over time (sinusoidal centrilobular dilation, hepatocyte atrophy, perisinusoidal-perivenular fibrosis) reduce oxygen diffusion and generate hypoxia, particularly in zone 3 (7). In heart failure patients, a supplementary decrease, even transient (minimum 20 minutes), in cardiac output and hepatic blood flow, often clinically undiagnosed, leads to hepatic necrosis, considering the liver has already been exposed to hypoxia due to passive hepatic congestion (6, 12).

IH/HH may also develop in the setting of acute heart failure, as it is the case in acute myocardial infarction, pulmonary embolism, cardiac tamponade. In these cases, liver ischemia is the main mechanism of cellular hypoxia and necrosis, following severe decrease in cardiac output, arterial hypotension and reduced hepatic blood flow.

Passive hepatic congestion and reduced arterial liver blood flow and “ischemia” lead to cellular hypoxia as final condition, in the setting of both chronic and acute heart failure.

FIGURE 2. Pathogenesis of hypoxic hepatopathy – adapted from Birrer *et al.* (13)

CVP=central venous pressure; LVF=left ventricular failure; MAP=mean arterial pressure; P_aO_2 =arterial oxygen pressure; RVF=right ventricular failure.

--- → indirect/secondary effect

→ direct/primary effect

Severe systemic hypoxia induced by respiratory failure (e.g., acute episodes of COPD, interstitial pulmonary fibrosis, etc) is the main cause of IH/HH in approximately 15% of cases. Severe arterial hypoxia (O_2 arterial pressure < 40 mmHg) significantly reduces oxygen delivery to hepatocytes and leads to cellular hypoxia. Systemic oxygen delivery falls below the critical level of 330 ml O_2 /min/ m^2 (normal level 720 ml O_2 /min/ m^2) (14). Cardiac output and hepatic blood flow are normal or even higher than normal, as opposed to chronic heart failure. Thus, there is no actual liver ischemia. In patients with chronic decompensated cor pulmonale, passive hepatic congestion may also play an additional role.

Shock, and especially septic shock, frequently seen in intensive care units, may lead to IH/HH. Septic shock prevalence varies from 11% to 16% and 23% (12, 13). The pathophysiologic mechanisms of IH/HH in patients with septic shock are different from cardiogenic shock. Cardiac output and hepatic blood flow are elevated, at least during the initial phase of septic shock. Hepatic hypoxia in septic shock is a result of hepatocytes increased metabolic needs, together with decreased O_2 extraction capacity, despite preserved O_2 saturation. Moreover, circulating endotoxins and inflammatory cytokines decrease the ability of hepatocytes to use oxygen and affect the microcirculation (15). Severe reduction in the cardiac output during shock may increase hepatic hypoxia.

Recently, the role of *ischemia/reperfusion process* in IH/HH injury is being discussed. Hepatocyte necrosis is present not only during ischemia but also during reperfusion (16). Oxidative stress and reactive oxygen species (ROS) may lead to injury either directly, by oxidation of proteins, lipids or DNA, or indirectly, by inflammatory cascade initiation and hepatocytes changes (17).

Hepatic cellular hypoxia is the final pathophysiologic process, as a result of ischemia (flow reduction), passive hepatic congestion, systemic hypoxia or other previously mentioned conditions. At the cellular level, decreased oxygen intake is followed by adenosine triphosphate (ATP) depletion and failure of energy dependent metabolic pathways and transport systems. Approximately two hours from the onset of ischemia, first hypoxic lesions appear

in the centrilobular region, but it takes three hours for the cellular injury to become irreversible (18). The cellular influx of Ca^{2+} signals non-reversible hepatocyte injury. Moreover, oxygen deprivation increases anaerobic glycolysis, lactate accumulation and decreased intracellular pH. Membrane transport is also affected, and potassium efflux in the extracellular space increases calcium storage in the cells. Cytosolic calcium activates proteases and phospholipases, which leads to a perpetual cellular membrane and cytoskeleton injury. Ischemia and probably apoptosis result in cellular death (12).

Elevated blood enzymes represent a marker of cellular death and IH/HH, and are a result of hypoxic injury of hepatocyte mitochondria and endoplasmic reticulum, especially in the centrilobular region. Cellular membrane changes allow for their systemic discharge. Similar enzymatic changes have been experimentally described through arterial hypoxia, hypoperfusion or endotoxins injury (13).

Clinical manifestations

Clinical manifestations in IH/HH have little specificity and are largely related to the underlying pathological condition (HF, respiratory failure, septic shock, postoperative status).

Typically, IH/HH develops in patients with congestive HF and congestive hepatopathy, with or without systemic congestion. Usually, the patient is admitted in the intensive cardiac care unit and has severe HF, with a recent/acute decompensation episode, after a prior HF standard treatment with diuretics, beta-blockers, renin-angiotensin-aldosterone system inhibitors. On admission, the patient may have a moderate-severe ill status with dyspnea, lethargy and drowsiness.

The response to maximal in-hospital medical therapy is poorer in these patients, with persistent congestion signs and/or low cardiac output and incomplete response to diuretics (diuretic-resistance).

The diagnosis of IH/HH, in the setting of congestive HF and systemic hypoperfusion, requires biological assessment and daily monitoring of several parameters.

The typical diagnostic pattern is based on sudden elevation in plasma aminotransferase and lactate dehydrogenase (LDH) level in the

setting of cardiac decompensation. The first 24-48 hours are characterized by an unexpected rise in AST levels shortly followed by an increase in ALT levels. Diagnostic values are 10 up to 250 times the normal upper limit (5, 12). However, the actual diagnostic cut-off limit may vary. Another characteristic of IH/HH is a higher level of plasma AST compared to ALT, as a direct result of higher concentration of AST in zone 3, the place where ischemic necrosis develops. There is a rapid decrease in AST plasma levels over 24-48 hours, whereas ALT takes longer (over one–two weeks) to return to normal (14).

Serum LDH is reported to be markedly elevated in IH/HH, sometimes even more than AST/ALT, yet it shortly returns to normal values. The early massive rise in LDH level is helpful in the differential diagnosis of IH/HH from viral hepatitis.

Additional liver tests abnormalities may occur in relation to IH/HH severity. The presence of elevated total and, more specifically, unconjugated bilirubin up to 2-3 mg/dL is a negative prognostic marker. Only one third of patients develop jaundice (13). One study found high levels of bilirubin being correlated with the arterial pressure level, but not with cardiac output (19). Other liver tests are within the normal range or slightly elevated – for example, alkaline phosphatase or INR values. An INR level >1.5 may precede the onset of acute liver failure.

Abnormal liver tests may be accompanied by other altered functional tests as a result of organ hypoperfusion. In a study including 182 patients, acute renal injury and elevated serum creatinine were present in 67% of cases, rhabdomyolysis in 46% of them, and 25% of patients developed ischemic pancreatitis (high levels of creatine-kinase and lipase, respectively) (20).

Half of patients with IH/HH in the setting of chronic liver diseases may also be at risk of developing hepatopulmonary syndrome, a complication that carries a poor prognosis (21).

The positive diagnosis of IH/HH relies on the currently accepted previously described criteria, which are based on characteristic biological tests and typical clinical signs of the underlying disease (cardiac or pulmonary disease, shock, prior subclinical liver disease).

There are several clinical conditions that have to be considered in the differential diagnosis of

rapid increase in aminotransferase level 10-20x the upper limit of normal:

- acute viral hepatitis or worsening of chronic viral hepatitis;
- toxic hepatitis (medication, drugs, acetaminophen etc);
- autoimmune hepatitis;
- transient biliary obstructive syndrome, with spontaneous gallstone obstruction;
- liver trauma.

In clinical practice, viral hepatitis is a frequent condition seen in patients with ischemic heart disease and heart failure.

Several biological elements are helpful to distinguish IH from viral hepatitis:

- persistent elevated plasma aminotransferase level in viral hepatitis, along with normal/minimum rise in LDH level;
- ALT/LDH < 1.5 during acute phase of hepatitis suggests IH over viral hepatitis (22);
- elevated serum creatinine is a relatively frequent finding in IH (induced by hypoperfusion), but not in viral hepatitis (6).

Moreover, certain imaging findings may add incremental value to IH diagnostic in difficult cases such as dilation of hepatic veins and inferior vena cava (23). Liver ultrasound might reveal hepatic changes, e.g., liver masses, which are accompanied by elevated levels of aminotransferase or other enzymes.

Outcome and prognosis

The prognosis of IH may range from complete regression of biological changes to short-time mortality, being more related to the underlying etiology and hemodynamic severity, hypoperfusion and hypoxia. Management should focus on correcting hypoperfusion and liver congestion, which are followed by regression of aminotransferase and LDH levels. There is a rapid decrease of AST level in 24-48 hours, while ALT and LDH plasma levels are reported to slowly return to normal values over a period of one to two weeks.

Complications may develop in patients with prolonged IH/HH, which they are often very difficult to manage. Acute hepatic failure may develop especially if IH/HH overlaps a chronic hepatopathy (hepatic cirrhosis, congestive chronic hepatopathy) (7, 24). In intensive care units with critically ill patients, IH/HH can be

associated with acute kidney injury (AKI) (25). In a recent study on 240 patients with IH/HH, 81% developed AKI, more than with half stage 3 AKI. In IH/HH patients, AKI correlated with underlying disease severity, especially shock, vasoactive drugs and elevated lactate level on admission (26).

Other IH/HH complications are severe hypoglycemia (4% of cases) but also hyperglycemia. Hepatopulmonary syndrome, less often seen in IH/HH as compared to liver cirrhosis, is associated with a worse prognosis of IH/HH. Once the liver function returns to normal, the hepatopulmonary syndrome is also reduced (27).

Approximately 50% of patients with IH/HH admitted in ICU have a severe prognosis. A recent review identified a 51% mortality rate (6). In another study on 38645 patients admitted to ICU, of which 1.46% developed IH/HH, the mortality rate was 41.1% (9). The causes of death are related to worse prognosis of the underlying disease and less often to acute liver injury. Pathological conditions associated with the highest mortality rate are cardiogenic shock and septic shock (8, 10).

Mortality predictors are older age and higher severity risk score related to the primary condition; elevated and persistent levels of aminotransferase and LDH; INR >2; worsened jaundice with bilirubin level >3 mg/dL; acute kidney injury; and vasopressors use (12).

Treatment principles

The main focus in IH/HH treatment addresses the underlying pathological conditions leading to liver dysfunction: severe heart failure, acute circulatory failure and respiratory failure. Therapeutic targets, as far as the liver is concerned, focus on hypoxia correction and increased oxygen supply with improved oxygen transport between blood and hepatic cells. Tailored therapeutic measures primarily target systemic hemodynamic correction by increasing cardiac output and arterial pressure, adequate vascular fluid replacement and volume expansion control, arterial hypoxia correction.

Acute or severe heart failure treatment may be the main concern. In patients with significant congestion and very low cardiac output, inotropes associated with diuretics (dobutamine plus

furosemide) increase cardiac output, reduce liver (and systemic) congestion and improve hepatosplanchnic circulation (14). Cardiogenic or septic shock requires specific measures: inotropes and vasoconstrictors; oxygen optimization; interventional treatment in acute myocardial infarction; antibiotics.

Dopamine use in renal or cardiac doses may lead to hepatic blood flow increase, although the benefits are uncertain (4). Inotrope medication may have potential detrimental effects on the already compromised cardiac function: arrhythmia, cardiac micronecrosis, death.

Excessive use of vasopressors (e.g., norepinephrine) in shock may worsen acute liver injury and IH/HH progression. Care must be taken when prescribing diuretics to avoid excess volume depletion, which may be responsible for reduced hepatic perfusion and zone 3 necrosis (12).

Other general measures focus on oxygen therapy, relative to hypoxia severity and tissue hypoperfusion, glycemic and hyperammonemia control.

Acute hepatic injury rarely represents the main clinical expression and its prognosis depends on the underlying pathological conditions leading to IH/HH. N-acetyl cysteine or other antioxidants failed to prove their efficiency (12).

Some patients with heart failure were already on statin treatment prior to IH/HH episode. They might be responsible for elevated aminotransferase level, but without the specific pattern of IH/HH. Most cardiologists chose to stop the treatment in these particular situations. A recent study on 851 patients admitted to ICU, of which 87 presented IH/HH, showed that IH/HH had developed in 11% of those without statin therapy vs. 5% of subjects on statins at admission (26). These results need further validation in future studies.

CONCLUSIONS

Ishemic hepatitis is a rare pathological condition, often difficult to separate from congestive hepatopathy. Accurate diagnosis is based on rigorous biological and clinical monitoring (rapid increase in aminotransferase and lactic dehydrogenase levels) in certain pathological settings. Critical patients are prone to develop more severe forms of IH/HH, frequently seen in acute heart failure, circulatory failure or shock. Patients

with a rapid regression of biological and hemodynamic parameters, as a marker of decreasing hepatic injury, have a better prognosis. However, the outcome of IH/HH in critically ill

patients may still remain poor, despite rapid diagnosis and maximal therapy. □

Conflicts of interest: none declared.

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