Hypoxic hepatitis : The point of view of the clinician

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Abstract

Hypoxic hepatitis better known under the terms of *ischemic hepatitis* or *shock liver* is the clinical manifestation of an acute liver cell necrosis consecutive to liver hypoxia. The clinical syndrome is defined as a massive but rapidly resolutive increase in serum aminotransferase activities (AT) occurring in a clinical setting of hemodynamic failure. Actually, when confronted to a case of massive increase in serum AT in the setting of cardiac or respiratory failure, the diagnosis of HH may be assumed without liver biopsy if another cause of hepatocyte necrosis such as viral hepatitis or drug induced hepatitis may be excluded. To our opinion, in these patients often aged and in poor general condition, it is particularly important to exclude herpes simplex virus infection and paracetamol intoxication. In case of doubt, a mere ultrasonography of the liver will be helpful. Indeed the majority of these patients will have a dilation of hepatic veins due to passive congestion of the liver. There is no specific liver therapy and the prognosis is poor depending on the severity of the underlying condition. In this point of view, we report what could be of interest for the hospital clinician. (Acta gastroenterol. belg., **2007**, 70, **214-216**).

Hypoxic hepatitis (HH), better known under the terms of *ischemic hepatitis* or *shock liver*, is the clinical manifestation of an acute and often extensive necrosis of centrilobular hepatocytes occurring in the clinical setting of hemodynamic failure. The biological hallmarks are a massive but rapidly regressive increase in serum aminotransferase (AT, $\geq 20 \times$ ULN) and lactic acid dehydrogenase activities and a rapid fall in prothrombin activitiy. Actually, when confronted to a case of massive increase in serum AT in the setting of cardiac or respiratory failure, the diagnosis of HH may be assumed without liver biopsy if another cause of hepatocyte necrosis such as viral hepatitis or drug induced hepatitis may be excluded. To our opinion, in these patients often aged and in poor general condition, it is particularly important to exclude herpes simplex virus infection and paracetamol intoxication. In case of doubt, a mere ultrasonography of the liver will be helpful. Indeed the majority of these patients will have a dilation of hepatic veins due to passive congestion of the liver.

Contrary to a widespread opinion, HH is not a rare liver injury. It is even the main cause of a massive increase in serum AT observed in hospital (1,2). In ICU, it accounts for 0.9-1.5% of all admitted patients (3,4). By contrast, it is true that this liver injury is rarely observed in Hepato-Gastroenterology units.

The patient at risk of developing HH is typically an old male patient suffering from cardiac or respiratory failure. Congestive heart failure (dilated cardiomyopathy) is the main underlying condition for HH. In our large series of 142 consecutive cases as well as from the review of the literature, cardiac failure accounted for 70% of all cases (3). Typically in these patients, HH is preceded by a period of deterioration of the cardiac condition and is triggered by an acute event, most often arrhythmia or acute pulmonary oedema. Respiratory failure is another frequent condition underlying HH. In our series, an acute episode or profound hypoxaemia superimposed on chronic respiratory failure was the cause of HH in 13% of all cases (3,5). In a recent Turkish series of 297 patients with chronic respiratory failure admitted to ICU for an acute episode of respiratory distress, 22 (7.4%) ultimately develop HH (6). The third main condition leading to HH, accounting for around 15% of all cases, is circulatory shock from septic or toxic origin (3). By contrast, shock from pure hypovolaemia due to haemorrhage rarely results in HH.

This large range of medical conditions exposing to HH clearly suggests that the haemodynamic mechanisms resulting in HH are multiple and generally associated. Hypoxic hepatitis is the result of an hypoxic necrosis of centribular hepatocytes due to an imbalance between the liver oxygen supply and demands. It may be caused by a decrease in the oxygen delivery to the liver due to ischaemia (fall in liver blood flow), hypoxaemia (decrease in the blood oxygen content) or severe anaemia (a decrease in the capacity of oxygen transport). It may also be caused by passive congestion of the liver as in right sided cardiac failure and by an incapacity of the liver cells to consume oxygen as in septic shock (dysoxia). In congestive heart failure, hypoxia of the liver is due to ischaemia and passive congestion of the liver (7), in chronic respiratory failure, HH is mainly due to severe hypoxaemia (5) and in circulatory shock, HH is due to dysoxia, injury of the liver microcirculation and increased liver demands of oxygen (8). It is interesting to point out that in respiratory failure as well as in septic shock, the hepatic blood flow is generally increased.

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However the increase in hepatic blood flow is not sufficient to prevent hypoxia of the liver. For these reasons, the term "ischaemic hepatitis" is too restrictive and should be avoided. Similarly, the terms "shock liver" should be also avoided because a shock state is observed in only 60% of the cases (for review see 3).

In the vast majority of cases, the diagnosis of HH is evident. The patient is in critical haemodynamic condition and the biological profile is suggestive. Nevertheless, HH may be tricky. In my experience, the most frequent trap was the absence of shock state. In several cases, the diagnosis of HH was considered, then turned down because of the absence of clinical shock. Another trap is the concealed consumption of drugs such as acetaminophen. Indeed, the biological profile of acetaminophen- induced hepatitis is similar to the one of HH. A systematic dosage of acetaminophen could be useful as this has been recommended for all cases of acute liver failure. Finally, the most difficult trap is undetected cardiac failure. Cardiac failure, even severe, may remain clinically undetected, particularly when the patient is treated by diuretics (9). In this setting, the patient is admitted to the hepato-gastroenterology unit with the suspected diagnosis of drug-induced hepatitis or even biliary problem because of the association of elevated liver enzymes and right upper quadrant pain (10). Often, the correct diagnosis and consequently the appropriate treatment are delayed and the prognosis is poor (10).

There are some particular forms of HH : peculiar progressions, peculiar groups of patients, peculiar circumstances (Fig. 1). For the peculiar progressions, it is interesting to point out that jaundice is not frequent in case of HH. A slight increase of bilirubin is a common finding but overt jaundice is observed in only around 15% of the cases (3). However cases of protracted jaundice have been reported probably favoured by renal insufficiency and sepsis (11). HH may also progress to acute liver failure with coma (12). According to the data from the US Acute Liver Study Group, HH accounted for around 5% of the cases (13). Among peculiar groups of patients, HH has been reported in children particularly after some cardiac surgical procedures such as Fontan procedure (14). Hypoxic hepatitis has been also reported in patients with cirrhosis in the course of concomitant haemorrhagic and septic shock. In this setting, the prognosis is very poor (15). Finally, HH may occur under some peculiar circumstances. Hypoxic hepatitis may be the terminal event of diffuse metastatic infiltration of the liver. This situation is particularly tricky because the malignant disease is generally not known until the onset of acute liver failure and because the liver imaging is not contributive showing no focal lesion of the liver (16). A hypoxic necrosis of centribulobar hepatocytes may also occur in severe grand mal seizures (17) and in heat stroke (18). In both these circumstances, the hepatic blood flow is probably increased despite hypotension, but the needs in oxygen of the liver are increased, the

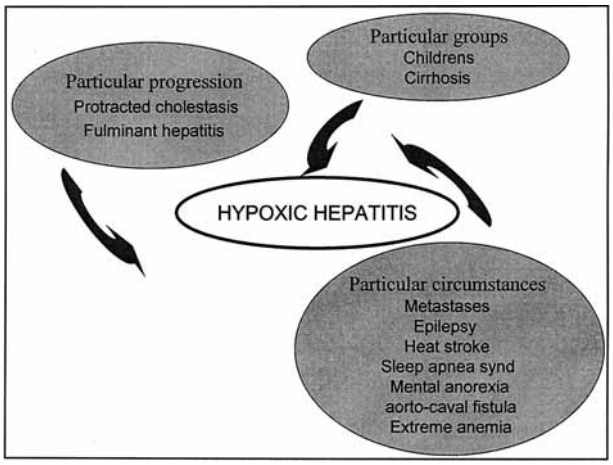

Fig. 1. — Particular aspects of hypoxic hepatitis

microcirculation is profoundly disturbed and the hepatocytes are unable to extract oxygen. More recently, hypoxic hepatitis has been reported in cases of mental anorexia (19), in very severe anaemia without hypovolemia (20,21) and in cases of aorto-caval fistula (22). In this last study reporting 135 cases of ruptured aortic aneurysm, it is interesting to point out that HH was only observed in 4 cases when an aorto-caval fistula was present. This suggests the additive role of an acute increase of presure in the caval vein leading to passive congestion of the liver.

Finally, HH is not merely an hypoxic necrosis. In animal studies, when the hepatic blood flow is interrupted or severely decreased, it is not at the time of ischaemia but at the time of reperfusion that the necrosis occurs. This phenomenon is recognized under the terms of ischaemia-reperfusion injury.

Actually, hypoxic hepatitis is probably a clinical manifestation of an ischaemia-reperfusion injury or better a hypoxia-reoxygenation injury. This is clearly suggested by animals experiments but it is also suggested by some clinical facts (23). In the early decades of the last century, investigators had already noted that the prevalence of centrilobular necrosis in patients dying of shock was higher when the duration of premortem shock had lasted for more the 24 hours (for review, see ref 23). So, they concluded that a long-lasting, protracted shock was needed. Actually, it is more logical to assume that patients could not survive as long as 24 hours in shock without benefiting from periods of reperfusion while the necrosis will occur. Conforting this hypothesis, in 47 patients rapidly dying from cardiogenic shock due to cardiac infarction (median of shock before death : 3 hours), we observed that an elevation of serum AT above $10 \times$ ULN was present in only 3 cases (6%) and that centrilobular necrosis was observed at immediate post-mortem liver biopsy in only 2 of 25 cases.

The hypoxia-reoxygenation injury also explain why Brunson et al observed an impressive increase of centrilobular liver cell necrosis in a 10-year series of

3229 autopsies from 1946 to 1955. In this series they were surprised to observe centrilobular liver cell necrosis in a 17/2107 (0.8%) cases during the 7 first years, but in 45/1122 autopsies (4%) during the last 3 years (24). The only explanation they were able to raise, was the increasing use of vasopressive drugs. They suggested that these drugs were provoking a vasospasm of the hepatic artery and they recommended to be careful with the use of these drugs. A more logical explanation is that these drugs allowed patients to survive longer and to experience some period of liver reoxygenation. Finally, hypoxia-reoxygenation injury also explains the midzonal liver cell necrosis (zone II of the acinus of Rappaport) frequently observed in experimental studies and sometimes reported in autopsies studies. In 1984, De La Monte *et al.* reported the pattern of liver cell necrosis in 214 liver specimens coming from patients dying in shock and they noted that in 8%, liver cell necrosis was not centrilobular but was midzonal (25). They could not provide any explanation for this phenomenon. At the light of today knowledge, we may assume that periportal hepatocytes were not destroyed because not sufficiently exposed to hypoxia, centrilobular hepatocytes were not destroyed because not reperfused and midzonal hepatocytes were destroyed because sufficiently exposed to hypoxia and then exposed to the front of reoxygenation.

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