

Nonalcoholic fatty liver disease. A pathological spectrum

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Nonalcoholic fatty liver disease (NAFLD) is becoming a public health problem in Western countries and is characterized by a wide spectrum of pathological lesions ranging from steatosis alone to steatohepatitis, advanced fibrosis, cirrhosis and even hepatocellular carcinoma. This disease, essentially due to metabolic syndrome, overweight and insulin resistance, may also be drug induced and secondary to intestinal bypass or resection, to total parenteral nutrition or to lipodystrophy. It is usually clinically asymptomatic and biochemical findings are mild and non specific (i.e., mild elevation of serum transaminases and γ -glutamyltranspeptidase, hyperlipidemia, hyperferritinemia). There is no alcohol intake, no serological evidence for viral infections, and the liver is hyperechoic if there is steatosis. Liver biopsy is done in order to : (a) differentiate steatosis alone from steatohepatitis ; (b) evaluate the severity of the lesions (i.e., grade and stage). In addition, the hepatic lesions probably reflect the pathophysiological mechanisms leading to NAFLD.

1. Liver lesions in nonalcoholic fatty liver disease

The spectrum of pathological lesions in NAFLD is hardly distinguishable from that of alcoholic liver disease. However, necroinflammatory activity and fibrosis are probably milder, Mallory bodies smaller and more poorly formed, and glycogen nuclei more prevalent in NAFLD (1, 5).

Hepatocellular steatosis is usually macrovesicular, made of large lipidic droplets displacing the nucleus at the periphery of the cell. Macrovesicular fatty change is occasionally associated with microvesicular steatosis, in which small lipidic droplets leave the nucleus at the center of the hepatocytes. Fatty change may either predominate around terminal hepatic veins or be diffuse within the hepatic lobule.

Steatohepatitis is defined by the presence of steatosis, polymorphous inflammatory infiltration containing lymphocytes and neutrophils, and by the existence of other hepatocellular lesions, mainly ballooning, hepatocellular death and cytokeratin aggregates forming intracytoplasmic Mallory bodies. Iron overload, if present, must be noted.

Fibrosis is perisinusoidal and initially predominates in centrilobular areas. Portal and periportal fibrosis may then develop, with progressive formation of fibrous bridges between terminal hepatic veins and portal areas, which may lead to cirrhosis. Cirrhosis is noted in up to 16 per cent of the patients at the time of diagnosis. At this stage, steatosis may have regressed or is no longer present, and lymphocytes may predominate in the inflammatory infiltration. It is noteworthy that NAFLD is frequently considered a major cause of cryptogenic cirrhosis.

Portal and periportal lesions have been increasingly recognized in NAFLD occurring in younger male patients of Asian, Hispanic or Native American descent, as well as in children in whom this finding has recently been debated. Such lesions may raise histological problems in the evaluation of liver lesions when NAFLD is associated with hepatitis C viral infection, or when autoantibodies are present in the serum, which is observed in up to 50 per cent of patients with NAFLD, thus raising the possibility of autoimmune hepatitis (1).

2. Assessing severity of nonalcoholic fatty liver disease

Since prognosis of NAFLD depends on the severity of the pathological findings, it is of importance to evaluate: (a) the degree of steatosis and necroinflammatory changes (i.e., grading) ; (b) the extent of fibrosis (i.e., staging). Scoring systems have been proposed (2, 4) and are mainly used in treatment trials and in natural history studies.

Grading semi-quantitatively evaluates steatosis from 0 to 3, lobular inflammation from 0 to 3, and hepatocellular ballooning from 0 to 2. The sum of these numbers gives a NAFLD activity score ranging from 0 to 8. There is no steatohepatitis if the score is 0 to 2 ; steatohepatitis is probable or definite if the score is 5 to 8, and is uncertain if the score is 3 or 4 (2). The overall grade may also be indicated as absence of activity, mild, moderate or severe grade (4).

Staging reflects the pattern and extent of fibrosis (2, 4). Stage 0 indicates that there is no fibrosis. In stage 1, there is mild (stage 1a) or moderate (stage 1b) perisinusoidal centrilobular fibrosis, or portal and periportal fibrosis only (stage 1c). Stage 2 is characterized by perisinusoidal fibrosis and portal and periportal fibrosis. Bridging fibrosis is observed in stage 3, and stage 4 corresponds to cirrhosis.

3. Prognostic factors in nonalcoholic fatty liver disease

Some **clinical and biological factors** seem to be predictive of the occurrence of severe fibrosis or cirrhosis, i.e., age more than 50 years, overweight, diabetes, serum alanine aminotransferase activity more than twice normal values.

The existence of **necroinflammatory activity** is also a factor of progression towards cirrhosis. Indeed, it has been shown that, in a series of patients with a mean follow-up of nine years, cirrhosis occurred in 3.4 per cent of the cases when steatosis alone or minimal necroinflammatory changes were noted on the first biopsy, whereas cirrhosis occurred in 24.7 per cent of the patients when there initially was moderate or severe steatohepatitis (3).

The role of **iron overload** as a prognostic factor has been suggested. Iron could induce lipidic peroxidation, thus favoring hepatocellular necrosis ; it also might activate stellate cells, thus stimulating collagen synthesis. However, this role of iron has been debated since no relationship between iron overload and occurrence of fibrosis has clearly been demonstrated in clinical studies (1, 5).

Hepatocellular carcinoma is a major complication of NAFLD, even if there is no cirrhosis (5).

4. Histopathological lesions and pathophysiological mechanisms of nonalcoholic fatty liver disease

Many of the lesions observed in NAFLD are probably explained by the complex network of pathophysiological mechanisms (5).

Hepatocellular steatosis may be induced by increase in free fatty acid supply to the liver and in hepatocellular synthesis of free fatty acids, insufficient increase in mitochondrial β -oxidation of free fatty acids, and impairment of triglyceride export.

In steatohepatitis, an additional event is necessary to explain hepatocellular lesions, inflammatory inflammation and fibrosis. This event is probably an increase in oxidative stress, in lipidic peroxidation and in production of cytokines. When formation of reactive oxygen species is stimulated by various factors such as insulin resistance, lipid peroxidation is activated and cytokines, as tumor necrosis factor α , interleukin-8, Fas ligand or transforming growth factor β , are produced. Both lipid peroxidation products and cytokines seem to be responsible for the histopathological lesions observed in steatohepatitis : (a) tumor necrosis factor α and Fas ligand trigger apoptosis ; (b) transforming growth factor β stimulates polymerization of cytokeratins and thus favors formation of Mallory bodies ; (c) interleukin-8 and lipid peroxidation products are chemoattractive for neutrophils ; (d) transforming growth factor β activates perisinusoidal stellate cells, and lipid peroxidation products increase their collagen synthesis, thus leading to perisinusoidal fibrosis and cirrhosis.

Hepatocellular carcinoma must be considered within the NAFLD spectrum, but the mechanisms of carcinogenesis are still unclear.

Références

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