

# Non-alcoholic steatohepatitis

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## Abstract

*Patients with chronic, moderately elevated liver enzyme concentrations without a diagnosis after a clinical, biochemical and radiological work-up are likely to suffer from non-alcoholic steatohepatitis or NASH. This possibility is further supported by the presence of obesity, hyperglycemia and hyperechogenic hepatic parenchyma. The diagnosis can be definitively made only by histological examination of a liver biopsy containing lesions suggestive of ethanol intake in a patient known to consume less than 40 g of alcohol/week. NASH is a common disease, with a prevalence around 1% of the general population similar to that of hepatitis C. The natural history remains to be studied, but it is not necessarily benign: cryptogenic cirrhosis in patients is a substantial number of probably end-stage NASH. The treatment is to lose weight for the overweight patients, to correct the biochemical abnormalities like hyperglycemia and hyperlipidemia and, if necessary to remove excess iron. Vitamin E and/or ursodeoxycholic acid may be helpful, but such therapies should be prescribed within clinical trials as their efficacies remain uncertain. Small trials have shown benefits of betaine and of a thiazolidinedione.*

## Keywords

Steatosis, hepatitis, aminotransferases, oxidative stress, cryptogenic cirrhosis, ursodeoxycholic acid, vitamin E

## Disease name and definition

Non-alcoholic steatohepatitis (NASH) is not a misnomer. This name reveals the important aspects of the disease. Coined by J. Ludwig *et al.*, in 1980 [1], it makes clear that NASH requires liver histology showing lesions suggestive of alcohol consumption and a convincing medical history to exclude that the patient consumes regularly drinks alcohol. For diagnostic purposes, alcohol consumption should be less than 40 g/week and liver sections should be carefully examined by an experienced

pathologist familiar with the histological staging and grading of NASH [2]. NASH covers a continuum from steatosis and mild inflammation - some opatients may even have normal serum aminotransferases - to established cirrhosis [3].

## Excluded diseases

NASH is, in a way, a diagnosis of exclusion. We do not yet have any biological test enabling a definitive diagnosis. Moreover, a precise assessment of alcohol consumption is crucial. For this purpose, an aspartate/alanine

aminotransferase (AST/ALT) ratio of less than 1 [4] or measurement of carbohydrate-deficient transferrin [5] might be helpful to distinguish NASH from alcoholic liver disease. A complete biological work-up for other liver diseases should be negative. Active viral hepatitis should be excluded based on serological and virological tests. It should be kept in mind that macrovesicular steatosis is frequently encountered in chronic hepatitis C. Autoimmune hepatitis is characterized by higher serum aminotransferase activities than the moderate elevation observed in NASH, elevated total IgG concentration and autoantibodies [6]. Primary biliary cirrhosis is rarely difficult to distinguish from NASH.

Some authors, based on several series of patients have used associated features, like obesity and diabetes mellitus, to suggest that a substantial fraction of patients with cryptogenic cirrhosis actually had NASH [7, 8]. At the cirrhotic stage the steatosis is often no longer present [9], perhaps as a consequence of the capillarization of hepatic sinusoids.

### Differential diagnosis

Few entities may pose diagnostic difficulties. NASH can affect obese teenagers [10]. The histology of a Wilson's disease with steatosis and Mallory bodies in a teenager may fulfill the criteria for NASH, but copper studies and genetic testing should be performed to reach the correct diagnosis. Hereditary hemochromatosis is now usually diagnosed based on genetic testing. Nonetheless, iron overload may play a pathogenic role in NASH [11] and an increased prevalence of mutations in the *HFE* gene has been reported in patients with NASH [12]. This latter possibility should not obscure the potential benefit of iron removal for these patients [52]. More subtle and sometimes artificial, is the distinguishing NASH from the syndrome reported by Moirand *et al.*, and characterized by hyperferritinemia and normal transferrin saturation with, which it shares several features [13]. A true  $\alpha$ -1 antitrypsin deficiency excludes the diagnosis of NASH, but variant phenotypes can occur in NASH patients [14]. Because of the high prevalence of NASH, the coincidental presence of a second liver disease should not be surprising.

### A brief history of NASH and its prevalence

In the 1980s, NASH was thought to affect mostly morbidly obese patients [15] who had undergone jejunoileal bypass [16, 17]. About a third of those patients developed a NASH with fibrosis [18] and several of them required liver transplantation after bypass surgery [19-21]. That situation is interesting from a pathogenic perspective, since

it combines exposure to lipopolysaccharides and cytokines from the excised bowel with rapid weight loss in a patient with an already fatty liver. Later, NASH was recognized in patients taking medication's like 4,4'-Diethylaminoethoxyhexestrol (DEAEH), amiodarone or perhexiline [22]. Those drugs appear to alter mitochondrial functions leading to fatty liver and lipid peroxidation [23]. Nowadays, probably the most frequent medication associated with NASH is tamoxifen [24]. Authors, reporting on several series underscored the high frequency of obesity, hyperlipidemia, diabetes mellitus and female gender of NASH patients [9, 25-27]. The entity was expanded in 1994 by Bacon *et al.*, who recognized the importance of NASH in the differential diagnosis of patients with abnormal liver enzymes [28] and NASH has since emerged as one of the most frequent liver diseases [29].

### Clinical description and diagnostic methods

Most of the patients are asymptomatic and the abnormal liver test results are often discovered fortuitously. The perturbation of liver function is chronic with serum aminotransferase activities usually less than 4-fold above the upper limit of normal. One of the major difficulties in the management of patients suspected of having NASH is the indication to perform a liver biopsy to obtain the diagnosis. This is an invasive procedure with a small, but definite risk of fatal complications. Ultrasonography provides valuable information suggestive of steatosis (hyperechogenicity) but fails to indicate the presence of inflammation [30]. It is important to recognize inflammation because liver steatosis without inflammation is a benign, non-progressive condition [31]. Patients with fat accumulation and ballooning degeneration in the liver biopsy have a liver-related mortality rate 10 times higher than patients with fatty liver with or without lobular inflammation [3]. Two studies were able to narrow the indication for a liver biopsy. Based on the data of 144 patients with NASH, Angulo *et al.* found that none of those younger than 45 years old with a body mass index (BMI) under 31 kg/m<sup>2</sup> and without diabetes mellitus had fibrosis in their biopsies [32]. Ratziu *et al.* found obesity of patients over 50 years old with a BMI superior to 28 kg/m<sup>2</sup>, triglycerides above 1.7 mmol/L and alanine aminotransferase more than twice the upper normal limit to be associated with septal fibrosis [33]. Moreover patients with none of these criteria or just one represented 30% of the collective and none had fibrosis in their biopsies [33].

### Etiology and pathogenesis

Macrovesicular steatosis alone cannot initiate NASH and, has a favorable long-term prognosis [31]. Other factors are necessary to trigger the inflammatory and fibrotic processes [34]. Oxidative stress is central to our current understanding pathogenesis. A fatty liver is particularly vulnerable to oxidative stress which provides a favorable environment for lipid peroxidation. The reasons for this oxidative stress can be multiple and non-exclusive: hyperglycemia, which by itself promotes the cellular production of reactive oxygen species, excessive hepatic iron accumulation [11], induction of the cytochrome P-450 2E1 [35] and perhaps even the endogenous production of alcohol [36].

### Evolution

In comparison to other liver diseases, little is known about the natural history of NASH. For example, the evolution of chronic hepatitis C, discovered in 1989, has been the subject of major articles in the literature including the data from thousands of patients. Without treatment, 33% of the patients with chronic hepatitis C have an expected median time to cirrhosis of less than 20 years [37]. Combining the available information, the progression of NASH seems to be comparable: 12% of the patients with NASH may progress to cirrhosis in 7 years [38]. Moreover, advanced NASH has been associated with a liver-related mortality rate 100 times higher than that of the general population [3]. The prevalence of obesity and diabetes is higher in patients with cryptogenic cirrhosis even when complicated by hepatocellular carcinoma than in patients with cirrhosis of well-defined etiology [53], [54].

### Treatment

There is no established treatment with an efficacy proven by randomized controlled trials. Common sense dictates weight loss for overweight patients. Even modest weight loss may improve hepatic function [39-40]. The weight loss should not be as drastic as after jejunoileal bypass, because its could lead to liver failure [41, 42]. Gastric bariatric surgery may attenuate NASH [43, 44]. Although treatment of the hyperlipidemia appears conceptually attractive, the results of the study addressing such treatment (clofibrate, 2 g/day for 12 month) were not encouraging [26]. The use of ursodeoxycholic acid may attenuate the biological abnormalities [26], was not found to do so in another pediatric study [45].

Based on our present understanding of NASH pathogenesis, one of the most promising

approaches is anti-oxidative therapy, especially vitamin E. Vitamin E stops the propagation of lipid peroxidation and has been shown experimentally to protect against liver damage [46, 47] and to prevent the activation of hepatic stellate cells [48]. Lavine published the results of a study supporting this approach in teenagers; unfortunately, no histological analysis was provided [49]. The data from pilot study, published in abstract form indicated a regression of histological abnormalities [50]. Whether vitamin E, alone or in combination with ursodeoxycholic acid, has a therapeutic value in case of NASH, needs to be determined with randomized controlled clinical trials providing histological data and with sufficiently a long follow-up.. Small trials have shown benefits of betaine [55] and of a thiazolidinedione [56]. Finally, patients with end-stage liver disease due to NASH can be transplanted but the disease may recur [51].

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