

METABOLIC LIVER DISEASES

REVIEW: Nonalcoholic steatohepatitis

JURGEN LUDWIG,* DOUGLAS B MCGILL† AND KEITH D LINDOR†

*Divisions of *Anatomic Pathology and †Gastroenterology and Internal Medicine) Mayo Clinic and Mayo Foundation) Rochester, Minnesota) USA*

Abstract Nonalcoholic steatohepatitis (NASH) is a reasonably well-defined clinicopathological entity; it has been reported more commonly in women than in men or children of both sexes and it appears to be most closely associated with obesity, diabetes mellitus and related abnormalities, such as hyperlipidaemia and hyperglycaemia. However, the association with female gender, obesity and diabetes may not be as close as suggested by the literature and an underlying condition cannot be discerned in all cases. The natural history of the disease is poorly understood; the associated biopsy features span a wide spectrum, reaching from uncomplicated, clinically non-progressive fatty liver (not NASH in a strict sense) to a slowly progressive fatty liver with inflammation and fibrosis, to steatohepatitis with submassive hepatic necrosis, which has a subfulminant course and is often fatal. Non-progressive fatty liver appears to be very common but is of little clinical importance. The slowly progressive form of the disease represents NASH as encountered by most clinicians and pathologists. It is a common liver disease in current practice; patients may present with cirrhosis and even HCC arising from steatohepatic cirrhosis. Subfulminant NASH has become exceedingly rare because many clinicians are now aware of the hazards of sudden weight loss, particularly in morbidly obese patients. Treatment options for NASH are still limited. The promotion of gradual weight loss in obese patients is the most widely recommended therapy but, unfortunately, this is very difficult to achieve. Avoidance of precipitous weight loss and careful control of diabetes mellitus are important and undisputed parts of patient management. Administration of UDGA as a treatment of NASH is still under study; it may be effective in some patients. The treatment of established steatohepatic cirrhosis does not differ substantially from that of other types of cirrhosis and includes orthotopic liver transplantation.

Key words: diagnosis, morphology, natural history, nonalcoholic steatohepatitis, terminology, and therapy.

HISTORY OF THE DISEASE

Fat people have fat livers. This has been known for about 40 years; even the appearance of inflammation and fibrosis in some of these fatty livers was described that long ago. However, the finding was largely ignored well into the 1960s. At that time, the condition that we now call nonalcoholic steatohepatitis (NASH) emerged from the spectrum of alcoholic liver diseases. The recognition of this apparently new disease resulted from the then popular intestinal bypass surgery for morbid obesity.²⁻⁹ In many patients who had been treated in this manner, a severe steatohepatic liver disease appeared as an unexpected and certainly undesired complication. The resemblance between the biopsy features observed in these patients and the well-known findings in alcoholic liver disease was soon noted.¹⁰ The prevailing opinion ascribed the hepatic lesions to post-operative nutritional abnormalities^{3,5,7} or to complications of bacterial overgrowth. These discussions failed to consider the observations of Zelman in 1958 and of Thaler who, in 1971, again mentioned the existence of a liver disease in non-alcoholic and non-surgical patients that resembled alcoholic liver disease.¹¹ It took almost another decade before other authors 12-15 confirmed this finding and established its association with obesity⁴ and diabetes mellitus.^{13,16} This delay may have happened, in part, because the published features of alcoholic hepatitis, such as the Mallory body, had been ingrained as being nearly pathognomonic for alcoholism and because apparent non-drinkers were simply regarded as closet alcoholics. The noted exceptions in post-bypass patients appeared to be an oddity in this regard. Discussions about various fatty liver diseases were further hampered by the absence of an established terminology. After the term nonalcoholic steatohepatitis was coined in 1980¹⁷ the condition came into better focus, as shown in the following paragraphs.

TERMINOLOGY AND CLASSIFICATION

Many names have been applied to the same condition, including fatty liver hepatitis,⁴ non-alcoholic steatonecrosis,⁷ non-alcoholic fatty liver disease in alcohol-like liver disease in non-alcoholics⁹ and non-alcoholic fatty hepatitis.²⁰ However, the name 'nonalcoholic steatohepatitis' has found the widest acceptance and is now used in most publications.²¹⁻²² The term is descriptive and can be transformed into an adjective as in 'steatohepatic cirrhosis' (Table 1); the now widely used abbreviation, NASH, is refreshingly brief. For a cogent terminology and classification, the name steatohepatitis should be used as a collective name for all conditions that manifest themselves by a common set of histopathological findings. Specific aetiological designations can be added, as shown in Table 1. Based on our own experiences and on evidence in the literature, we would like to propose a clinical and prognostic classification as shown in Table 2; this is discussed further under 'Prevalence and Natural History'.

Table 1 The terminology of steatohepatitis

Steatohepatitis
Alcoholic
Acute and/or chronic (synonym: alcoholic hepatitis)
Nonalcoholic
unspecified or chronic, with or without putative aetiological association, such as chronic nonalcoholic obesity related steatohepatitis
Of unknown etiology
unspecified or chronic
Steatohepatitic cirrhosis
Alcoholic (synonym: alcoholic cirrhosis)
Nonalcoholic
with or without putative aetiological association, such as nonalcoholic obesity related steatohepatitic cirrhosis
Of unknown etiology
Chronic (by definition)

MORPHOLOGY

The morphological features of NASH are principally indistinguishable from those of alcoholic liver disease. Macrovesicular fatty changes, fat cysts, Mallory bodies in zone 3, spotty necroses and inflammatory infiltrates with admixed neutrophils are the most typical findings. Fibrosis arising from the terminal hepatic venules and perisinusoidal spaces connotes chronicity and, thus, is a most important finding. In early stages of chronicity, fibrosis may not be noticeable without a connective tissue stain. This is one of the many reasons why such a stain should be prepared for all liver biopsy specimens in the work-up of non-neoplastic diseases. The same holds true for iron stains because in NASH, as in alcoholic liver disease, these stains commonly are positive for hepatocellular haemosiderin,²² which may mean that an evaluation for associated genetic haemochromatosis is indicated. Although individual cases are indistinguishable, large cohorts of alcoholic and nonalcoholic steatohepatitis differ in that the necro-inflammatory changes in nonalcoholic patients tend to be milder. If biopsy samples can be compared over time, NASH generally appears to progress slower than its alcoholic counterpart. Obviously, this does not hold true for the rare cases of subacute --(subfulminant) NASH that runs a course very similar to -fatal alcoholic hepatitis. Subacute NASH may even be associated with hepatocanalicular cholestasis, a feature that is quite rare in chronic NASH and, generally, would be more typical for severe alcoholic hepatitis. Thus, as a group, chronic NASH tends to be milder than alcoholic liver disease, but in individual cases the distinction between the two conditions still must be made clinically.

The number of conditions that may simulate steatohepatitis is rather limited. The most important liver diseases in this regard are chronic hepatitis C,²³ other types of chronic hepatitis with coincidental fatty changes (e.g. autoimmune hepatitis with steroid

Table 2 A clinical classification of nonalcoholic steatohepatitis

Clinical designation and prevalence	Duration and prognosis	Biopsy findings
Nonalcoholic fatty liver+ (very common)	Generally non-progressive with good prognosis	Fatty changes with only minimal or no inflammation and no fibrosis
Subacute (subfulminant) NASH (very rare)	May progress to hepatic failure in <6 months	Fatty liver with submassive hepatic necrosis
Chronic NASH (common)	Slowly progressive~ generally lasting >10 years, ending in cirrhosis in some cases	Fatty changes with mild to moderate inflammation and fibrosis evolving from zones 3

*Not strictly a 'hepatitis') but the condition is included here because inflammation may be missed because of sampling variations and because nonalcoholic fatty liver may merge imperceptibly into steatohepatitis.

NASH, nonalcoholic steatohepatitis.

induced fatty changes) and rare cases of focal fatty change with associated inflammation.²⁴ Chronic hepatitis C with Mallory-type inclusions may be particularly difficult to distinguish from steatohepatitis. It is helpful to remember in such cases that chronic viral or autoimmune hepatitis is a portal or periportal hepatitis (inflammation in zone 1), whereas steatohepatitis is a

centrilobular hepatitis (inflammation in zone 3). Unfortunately, these important distinguishing features are not always sufficiently apparent or they are not correctly diagnosed (e.g. when pathologists fail to identify the hepatic artery branch and mistake an inflamed centrilobular scar for a portal tract). Focal fatty changes may also be mistaken for steatohepatitis and, thus) it is very important that pathologists are informed if a sample came from a focal lesion. Finally, Wilson's disease has features of steatohepatitis, primarily in its early stages. Therefore, copper studies should be done if patients are young or if Wilson's disease is considered for other reasons.

PATHOGENESIS

Early experience with morbidly obese patients who had intestinal bypass surgery suggested that steatohepatitis was a complication of the procedure (e.g. due to protein malnutrition⁷ or bacterial overgrowth⁹). However, subsequent observations have provided at least circumstantial evidence that the hepatic abnormalities are caused by metabolic changes associated with precipitous weight reduction, largely unrelated to the means by which weight loss had been achieved. Thus, subacute or chronic steatohepatitis was found not only in some patients who had intestinal bypass surgery but also in patients who had other forms of weight-reducing surgery, such as gastric bypass and gastroplasty²⁵ or biliopancreatic diversion.²⁶ Most important in this context is the observation that even without any surgical intervention, precipitous weight loss in morbid obesity, for instance after fasting,⁷ can cause subfulminant or chronic disease. Most patients with these complications probably had pre-existing NASH; the sudden weight loss may merely aggravate the chronic disease sufficiently to cause submassive hepatic necrosis.

It is now clear that obesity associated with NASH does not need to be severe and, indeed, in some patients neither obesity nor any other reported associated condition can be found.²² Nevertheless, most patients with NASH are obese, albeit not in the morbid range. The second most common association is adult-onset diabetes mellitus. Although many patients with diabetic NASH are also obese, the association may occur with diabetes alone. In rare cases, steatohepatitis even seems to antedate the manifestations of diabetes mellitus.²³ Other manifestations, such as hyperlipidaemia, probably belong in the same category.² Fatty changes or steatohepatitis in malnutrition from bulimia,³⁰ after coeliac disease or following short bowel syndrome³²⁻³³ have not been studied sufficiently to obtain a meaningful comparison with obesity related NASH. The same holds true for drug-induced steatohepatitis,³⁴ some manifestations of total parenteral nutrition,³¹ the two reported cases of limb lipodystrophy with steatohepatitis, the focal steatohepatitis in a liver cell adenoma³⁶ or the subcapsular steatohepatitis after intraperitoneal insulin administration.³⁷

The similarities between alcoholic and classic nonalcoholic steatohepatitis suggest that the histological changes have a common pathogenesis. For example, the same genetic susceptibility may be present in both patient groups. It is interesting to speculate that the same 20% of alcoholic patients who develop significant liver disease would develop NASH if they were non-drinkers but were obese or diabetic. We are not aware of studies that would have specifically tested this hypothesis. Several possible pathogenetic mechanisms have been proposed. Thus, NASH may be a result of decreased insulin sensitivity in diabetic and obese patients leading to hyperinsulinaemia with toxic accumulation of free fatty acids. Similarly, endotoxaemia may lead to this type of hepatocyte injury because it triggers the production of free radicals.⁴¹ Finally, a defect in the function of peroxisomes has been under discussion.⁴² These and other proposed pathogenetic mechanisms are not mutually exclusive.

PREVALENCE AND NATURAL HISTORY

Little is known about the prevalence or natural history of NASH. Biopsy evidence is available primarily from the relatively few symptomatic patients. Sequential biopsies in patients with NASH are particularly uncommon. If biopsy specimens had been obtained, it is often difficult to determine from the morphological descriptions whether fatty changes or steatohepatitis had been present. Furthermore, NASH may be missed because by the time biopsies are done, most fatty changes may have disappeared so that the hepatitis or cirrhosis is considered cryptogenic. Nevertheless, some rough estimates can be made. For example, in a study of 4613 male Japanese company employees, 534 were moderately obese and almost half had hepatic steatosis as judged by computed tomography.¹³ Twenty-four per cent of these obese patients had abnormal alanine aminotransferase (ALT) activities. A subsequent study revealed ultrasonographic evidence of fatty livers in 14% of 2574 patients from Okinawa. Fatty change was most common in persons between 40 and 49 years of age. Obesity was the strongest associated factor in both sexes; however, in males alcohol also was a strongly associated factor.⁴⁴ In an autopsy study,⁴ NASH was found in 18.5% of markedly obese patients and in 2.7% of lean patients.

As stated, most cases of NASH have been described in women with or without diabetes, but recent studies²² suggest that the condition is also common in men and that obesity, hyperlipidaemia and glycaemia are not prerequisites. Non-alcoholic fatty liver without appreciable inflammation or fibrosis appears to be the most common manifestation of NASH, although by strict criteria it is not a hepatitis. Thus, in a recent study of 14 patients with obesity and diabetes-related NASH and a median follow-up of 11 years (range 7-16 years), none developed evidence of progressive liver disease.⁴⁵ However, transition from the uncomplicated non-progressive fatty liver to slowly progressive NASH may be difficult to discern because biopsy samples are often reviewed without the use of the tell-tale connective tissue stains and because sampling variations exist, as in most other liver diseases. The development from NASH to steatohepatic cirrhosis was clearly documented in a study of 42 patients²⁹ who had been observed for 1.5-21.5 years (median 4.5 years); two patients developed cirrhosis that, in one instance, was complicated by hepatocellular carcinoma (HCC). The degree of obesity, hyperlipidaemia and hyperglycaemia did not correlate with the severity of the histological changes. Although some studies show progression in NASH to be rare and, if it occurs, very slow, the Mayo Clinic experiences with NASH suggest a less favorable scenario. Thus, in the past 5 years we have treated many patients with NASH

who had unequivocal biopsy evidence of prominent fibrosis or cirrhosis. Also at our institution, seven patients with NASH cirrhosis underwent orthotopic liver transplantation in the decade between 1985 and 1995 (1.6% of 447 transplant patients with cirrhosis); the disease was complicated by HCC in one of seven cases. Thus, we consider the various clinical types of NASH (Table 2) part of a spectrum that is heavily weighted towards the benign and often non-progressive or only slowly progressive disease manifestations.

CLINICAL DIAGNOSIS

Most commonly, patients ultimately diagnosed with NASH present with abnormal aminotransferase activities, which have been identified during the course of routine screening. In other instances, the condition is recognized following treatment with lovastatin, isoniazid, tamoxifen, nicotinic acid, methotrexate and other drugs that may or may not have anything to do with the observed histopathology. Physicians prescribing these drugs are advised to follow their patients carefully and to discontinue drug treatment if abnormal aminotransferase values are identified.

Some patients with NASH present with fatigue and vague right upper quadrant pain. It is extremely difficult, if not impossible, to determine whether these symptoms have any relationship to liver findings. The physical findings are usually unhelpful, although an occasional patient has classic smooth hepatomegaly. Most often the liver is palpable in the right upper quadrant beneath the costal margin, but estimates of liver size based on this physical finding are generally unreliable. Splenomegaly is absent, as are stigmata of chronic liver disease. The laboratory findings feature increased values for one or both of the aminotransferases, aspartate aminotransferase (AST) and ALT. The values are only modestly increased, but occasionally the increase may be five-fold or more. Values for alkaline phosphatase are only rarely above 1.5-fold normal. Immunoserological markers are negative apart from antinuclear antibodies (ANA), which may be positive in titres up to 1:80 in approximately 25% of cases.

Unfortunately, no laboratory studies are characteristic of NASH. Some interest has recently been centered on cholinesterase determinations,⁴⁶ but more data are needed. It remains impossible to eliminate ethanol abuse from consideration based on any specific laboratory test. Determination of γ -glutamyl transferase yields nonspecific results and should no longer be considered relevant in this context. The role of desialated transferrin⁴⁷ remains to be determined. Perhaps this is the most promising test, but many hepatologists are skeptical. The presence of hyperlipidaemia and hyperglycaemia make NASH a more likely diagnosis.

Ultrasound studies often reveal a coarsened echo-texture or 'bright' liver. Unfortunately, this echo-texture is not specific for fat alone, as a fibrotic liver can give the same appearance. The degree of steatosis also influences the ultrasonographic appearance and there is an element of subjectivity in each reviewer's threshold for recognizing 'brightness'. There are patients whose ultrasound examination is essentially normal but who have steatohepatitis on biopsy. In these instances, the degree of fatty infiltration appears to be insufficient to influence the image. Histological examination of a liver biopsy by an experienced pathologist is the essential diagnostic element, recognizing that NASH and alcoholic liver disease cannot be distinguished with confidence. In practice, it seems unreasonable or at least unnecessary to subject all patients to biopsy if the setting and clinical features are sufficiently persuasive to diagnose NASH.

TREATMENT OPTIONS

Treatment for this condition usually revolves around weight reduction, even though the benefits of weight loss have been inconsistent. A single report describes a patient whose biopsy showed a fatty liver that reverted to essentially normal following an 11 kg weight loss over 1 year.⁴⁸ In another study, five obese patients stopped eating for some time and lost 14-30 kg within 1 month. The hepatic fat content decreased in three of these patients, but fibrosis became more prominent in four of the five. In another series, 14 patients maintained a mean weight loss of nearly 65 kg for 1.5 years and in more than half liver biopsy findings normalized.⁵⁰ Thus, it seems that substantial weight loss, particularly if gradual, may lead to improvement in liver histology. Unfortunately, however, achieving and maintaining weight loss has been virtually impossible for many of these patients.⁵¹ Nevertheless, an attempt at gradual weight loss is a likely useful first step in the management of these patients. As stated earlier, rapid weight loss is potentially hazardous, particularly in the presence of morbid obesity. In patients with hyperlipidaemia and diabetes, good laboratory control is always recommended, but seldom effective, in reversing steatohepatitis.

Medical therapy directed specifically at the liver disease has been rarely evaluated in this group of patients. In a pilot study performed at the Mayo Clinic, clofibrate was used in 16 patients with NASH and hypertriglyceridaemia. Clofibrate was chosen for its properties to lower lipids and to stabilize peroxisomes. Unfortunately, the use of clofibrate for 1 year did not improve liver biochemistry or histology.¹²

In a concurrently conducted pilot study in patients without hypertriglyceridaemia but with histological evidence of NASH, ursodeoxycholic acid (UDCA) appeared promising. Ursodeoxycholic acid, the seven beta epimer of chenodeoxycholic acid, was shown to be of substantial benefit in patients with other liver diseases, such as primary biliary cirrhosis. The drug has been used in the treatment of other liver diseases as well.

Ursodeoxycholic acid reduces cholestasis and has immunomodulatory properties.⁵³⁻⁵⁴ Furthermore, UDCA may stabilize cell membranes and protect against cytotoxic insults that could be potentially important in patients with NASH.⁵⁵ In our pilot study, 24 patients were treated with UDCA (12-15 mg/kg per day). Two-thirds of patients were female and obesity was present in approximately 60%, while 38% of patients had diabetes. Ursodeoxycholic acid treatment reduced the activity of ALT, γ -glutamyl

transferase and alkaline phosphatase along with the grade of fat in follow-up liver biopsy specimens.⁵² Because of these promising effects, a randomized trial has been organized to evaluate the role of UDCA in the treatment of NASH.

The treatment of late-stage steatohepatic cirrhosis does not differ substantially from that of other types of cirrhosis and may include, as stated earlier, orthotopic liver transplantation.

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