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CLINICAL PERSPECTIVES

Nonalcoholic fatty liver disease: is all the fat bad?

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Abstract
Nonalcoholic fatty liver disease is now a major cause of liver disease in developed countries, largely as a result of an epidemic of obesity, diabetes and sedentary lifestyles. This has resulted in raised clinical awareness and diagnostic refinement. The entity encompasses several histologic patterns from benign steatosis to nonalcoholic steatohepatitis, the latter having a significant risk of progressive fibrosis and the development of cirrhosis. Laboratory tests and imaging are not able to distinguish steatosis from steatohepatitis, which requires liver biopsy. However following an assessment of several risk factors, patients can be stratified for the potential risk of fibrosis, allowing the rational use of liver biopsy. This review will describe the various patterns of nonalcoholic fatty liver disease and relate this to disease pathogenesis and progression. Strategies for management, including experimental interventions, will be discussed. (Intern Med J 2004; 34: 187–191)

Key words: Steatohepatitis, steatosis, cirrhosis, pathogenesis.

INTRODUCTION

Since Ludwig *et al.* described a cohort of patients with biopsy changes resembling alcoholic liver disease but who did not drink excess alcohol,[1] nonalcoholic steatohepatitis (NASH) has become well known as a cause of liver disease. Moreover, as obesity and type 2 diabetes increase to near-epidemic levels, the disorder has become the subject of increased focus and diagnostic refinement. The disease spectrum has widened with the recognition that most patients develop a non-progressive lesion, usually steatosis, and that true NASH occurs in only a proportion. The entire spectrum of disorders is now referred to as nonalcoholic fatty liver disease (NAFLD) of which NASH is a subgroup with specific, diagnostic features and a greater risk of progressive fibrosis and cirrhosis.

This review will outline the spectrum of lesions seen in NAFLD, relate these to the prognosis, and provide a framework for management.

NOMENCLATURE

The published literature on fatty liver disease has been complicated because of variable diagnostic criteria used in different laboratories, resulting in confusion about the natural history and exactly what constitutes true NASH (reviewed by Brunt,[2]). Following the initial description, which applied quite strict diagnostic criteria that paralleled those of alcoholic liver disease, there developed a tendency to use the term NASH to refer to a biopsy showing steatosis and any form of inflammation. Recent studies on prognosis and aetiopathogenesis have shown that this was erroneous.

A study by Matteoni *et al.* published in 1999, provided specific histological patterns and correlated these with long-term outcomes.[3] The categories that they described were as follows:

- Type 1 Steatosis alone
- Type 2 Steatosis + non-specific inflammation
- Type 3 Steatosis + hepatocyte ballooning
- Type 4 Steatosis + ballooning + Mallory's hyaline or fibrosis.

The categorisation proved useful for prognostication (Table 1). Generally, unless the typical alcohol-like changes of ballooning, Mallory's hyaline or fibrosis were present, NAFLD was self-limited. Patients with steatosis, or steatosis and non-specific inflammation were unlikely to progress to cirrhosis, whereas those with true NASH showed cirrhosis in over 20% of cases and liver-related death in 5–13%. Largely as a result of the study by Matteoni *et al.*, there has been a change in the use of the term NASH. Many, but not all would now agree that as well as steatosis and inflammation, hepatocyte ballooning should be present in NASH, and at least some neutrophils are generally seen within the inflammatory infiltrate.

PREDISPOSING FACTORS

Although NAFLD may occur in non-obese patients[4,5] most cases develop in the context of obesity and/or type 2 diabetes.[6] From the outset, it is useful to remember

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Table 1 Types of NAFLD (after Matteoni *et al.*[3])

	Histological pattern	Prognosis
Type 1	Steatosis only	Benign
Type 2	Steatosis + inflammation	Benign
Type 3	Steatosis + hepatocyte ballooning	Some progress
Type 4	Steatosis + fibrosis or Mallory's	Some progress

NAFLD, nonalcoholic fatty liver disease.

that many patients with these conditions develop NAFLD but only a proportion, probably around 10–15%, develop true NASH, and only a proportion of these (estimated at around 20–30%) develop progressive fibrosis and cirrhosis. Translated to the general population, the incidence of NAFLD is estimated at around 20% with NASH occurring in around 2–3%.[7,8]

Underlying most cases of NAFLD is insulin resistance with a resultant increase in circulating insulin levels. Obesity and/or diabetes are usually the conditions underlying this and NAFLD is an important facet of the metabolic sydrome.[9] Insulin resistance promotes increased peripheral lipolysis resulting in the delivery of increased amounts of free fatty acids to the liver. Free fatty acids undergo mitochondrial β oxidation, peroxisomal β oxidation, or re-esterification to triglycerides, which are packaged as very low-density lipoproteins (VLDL) and secreted by the liver. Triglycerides accumulate in the liver, producing steatosis, when the ability to make or secrete VLDL is exceeded. On its own, steatosis is relatively benign, but some patients develop additional oxidative stress. It is unclear why this occurs, but several mechanisms have been implicated. Insulin resistance produces intrahepatic oxidative stress by increasing mitochondrial fatty acid β oxidation. In addition, the cytochrome p450 system, tumour necrosis factor and hepatic iron stores have also been identified as potential sources of free radicals in the liver in NASH. The elaboration of reactive oxygen species leads to lipid peroxidation, hepatocyte injury and collagen production. Genetic differences between individuals are also postulated to be of importance.[10]

NASH also develops as a result of several rare but well-characterised disorders, listed in Table 2. Cases of NASH as a result of drugs such as amiodarone, jejunoileal bypass and total parenteral nutrition with probable micronutrient deficiency[11] are more likely to be progressive, probably as a result of greater oxidative stress and profibrogenic cytokine release. Importantly, amiodarone-induced NASH may progress after drug cessation.

Table 2 Causes of NASH

Obesity
Metabolic syndrome (syndrome X)
Insulin resistance – lipodystrophy
Nutritional deficiencies
Total parenteral nutrition
Drugs (tamoxifen, amiodarone, perhexiline)
Jejunoileal bypass
Rapid weight loss

NASH, nonalcoholic steatohepatitis.

NATURAL HISTORY OF NAFLD AND NASH

It is now clear that steatosis is common and benign, but true NASH is less so. When carefully defined, NASH has a prevalence of 2–3%[8] and identifies the subgroup of patients at risk of progressive fibrosis. The early descriptions of NASH pointed to obese patients, often females with diabetes who were typically affected. However, the spectrum has widened and NAFLD is now recognised in a wide range of patients including children and male patients with normal weight and without abnormalities in either glucose or lipid metabolism.[6]

Who, then, is at risk of progressive NASH with fibrosis and cirrhosis? Not surprisingly, increasing severity of obesity correlates with fibrosis[12] and this was shown to be independent of concurrent diabetes and age.[13] The incidence of NASH rises to over a quarter of severely obese patients and, in one study, over 40% of these affected patients had advanced septal fibrosis or cirrhosis.[14] Age (>45–50 years) plays a role, and diabetes is also an independent risk factor for more severe NASH.[13] Conversely, patients under 50 who are in the overweight but not obese range and who have modest elevations of transaminases of up to twice normal do not appear to be at risk for fibrosis.[12] Hypertension as part of the metabolic syndrome and higher levels of alanine aminotransferase (ALT)[14] are linked to more severe fibrosis, and it appears that when individual risk factors are combined the chance of NASH and fibrosis increases.[12,14]

The potential for NASH to result in end-stage liver disease has been highlighted recently by evidence suggesting that NASH may underlie many cases of cryptogenic cirrhosis.[15] The absence of steatosis in advanced cirrhosis as a result of NASH is well recognised[16] and risk factors for NASH are more frequent in patients transplanted for cryptogenic cirrhosis. NAFLD develops in almost half of the liver grafts of these patients, but NASH develops in only 7–16%.[10]

There is a dearth of information about regression of NAFLD and NASH because of the difficulty in obtaining serial biopsies. Untreated NASH may be static but rarely improves spontaneously.[8] Steatosis regresses with weight loss, but less is known about the inflammatory activity

and fibrosis. Rapid weight loss, whilst improving steatosis, worsens steatohepatitis[17] and is the rationale for recommending gradual weight loss. Determining the natural history of NASH and fibrosis after clinical intervention may require the development of non-invasive detection methods before large-scale, prospective studies can be performed.

NAFLD AND A SECOND LIVER DISEASE

The coexistence of a second liver disease in the presence of steatosis may provide a source of oxidative stress that could exacerbate liver injury and transform benign hepatic steatosis into a potentially progressive lesion.[10] Studies in chronic hepatitis C provide supportive evidence for this. Obesity also worsens the outcome of alcoholic liver disease,[18] not surprisingly in view of shared pathogenic pathways. Drug-induced liver disease may be exacerbated by obesity, and this has been proposed for tamoxifen and methotrexate.[11]

Other associated disorders are less clearly defined. Iron, which is a source of oxidative stress, has been suggested as a cofactor in disease progression in NASH[19] but subsequent studies have failed to confirm this. Interestingly, despite the lack of a clear association with fibrosis, there does appear to be an increased frequency of HFE mutations in patients with NASH. A significantly higher frequency of heterozygosity for alpha-1-antitrypsin was also shown[20] and is proposed as a potential aggravating factor.

CLINICAL AND LABORATORY FINDINGS

Although steatosis can be detected by non-invasive imaging, steatohepatitis can only be reliably diagnosed on liver biopsy and this is a major problem.

Patients commonly present with an asymptomatic elevation in transaminases, typically of mild to moderate degree. Symptoms are absent or vague, and right upper quadrant discomfort and lethargy are described.[16,21] Apart from hepatomegaly, physical signs are generally absent unless cirrhosis has supervened. When viruses, drugs and auto-immune diseases are excluded as causes, up to 90% of transaminase rises are a result of NAFLD.[21]

Laboratory findings

The ALT level characteristically exceeds the aspartate aminotransferase (AST) level (ALT/AST > 1) but this relationship can reverse in the presence of severe fibrosis and cirrhosis.[13] It should be remembered that in some patients, liver function tests remain within the normal range. Serum ferritin is elevated, sometimes significantly, in over half of the patients and in a minority the transferrin saturation is also increased; this generally does not correlate with an increased hepatic iron concentration. The frequency of heterozygous HFE gene mutations, both C282Y and H63D, appears to be increased in NASH, but again this does not correlate with significant hepatic iron deposition.

Imaging

Imaging is able to detect fatty change in the liver[22] but cannot reliably detect ballooning, steatohepatitis or fibrosis. Diffuse echogenicity is seen on ultrasound but is also a feature of fibrosis. The sensitivity of ultrasound is reduced with lesser degrees of steatosis.

THE ROLE OF LIVER BIOPSY

The liver biopsy remains the gold standard for diagnosis and has an important role in both detecting steatohepatitis, as well as staging any fibrosis present. As discussed above, the correct categorisation provides important prognostic information, and apart from biopsy there is no reliable way to distinguish between benign steatosis and potentially progressive NASH. Moreover, at present, biopsy is the only way to quantify any fibrosis that is present. The histological features of NAFLD and NASH are distinctive, and often allow its diagnosis even when a second disease is present.[2,10]

Who should be biopsied?

This remains controversial, and needs to be individualised (Table 3). Ratziu *et al*. found that a score giving one point to each of four variables – body mass index (BMI) (>28 kg/m^2), age (>50 years), ALT (≥2 × normal) and triglycerides (>1.7 mmol/L) – indicated those patients for whom biopsy should be considered.[12] A BAAT (BMI, age, ALT, triglycerides) score of 0 or 1 was never associated with septal fibrosis, whereas increasing scores over 1 correlated with the risk of fibrosis. Others have found severe obesity (BMI> 35 kg/m^2), hypertension, diabetes and a reversed AST/ALT ratio of >1 to be additional risk factors and, like the study by Ratziu *et al.*, found that two or more risk factors heightened risk.[13,14]

In an at-risk obese or diabetic patient with elevated liver function tests, one approach prior to liver biopsy, is to attempt normalisation of liver enzymes with gradual weight loss, exercise and correction of metabolic abnormalities. Over a three month period liver enzymes may return to normal, and biopsy may be reserved for those with persistently elevated tests.

Histological features

Patients with NAFLD develop mild to severe steatosis that preferentially affects zone 3 hepatocytes. It can become less apparent or even disappear late in the disease if cirrhosis develops.[16] When steatosis is accompanied by non-specific aggregates of lymphocytes and macrophages, steatohepatitis is not diagnosed (Fig. 1a). A diagnosis of NASH requires steatosis plus either hepatocyte ballooning or Mallory's hyaline or subsinusoidal fibrosis

Table 3 Patients at higher risk for NASH and fibrosis

Severly obese (BMI>35 kg/m^2)
Older age (>45 years) + diabetes/obesity or AST/ALT ratio >1
Younger age (<45 years) + diabetes/obesity and AST/ALT ratio >1

NASH, nonalcoholic steatohepatitis; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

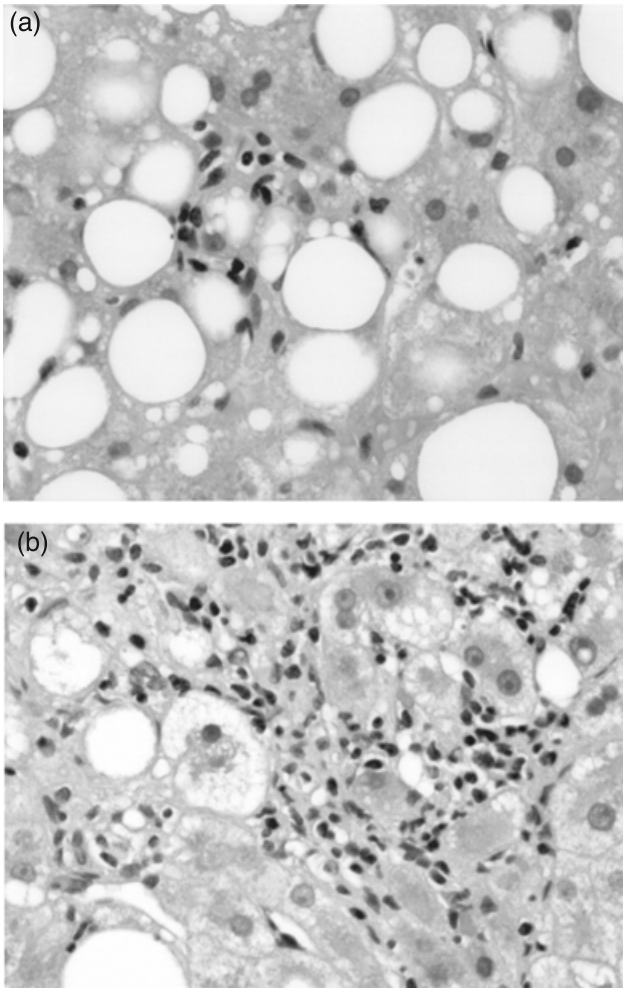

Figure 1 Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). (a) The presence of steatosis and non-specific lymphocytic infiltrates is not sufficient to diagnose steatohepatitis. (b) True NASH also has hepatocyte ballooning, which is usually accompanied by neutrophil infiltration. The diagnosis can also be made in the absence of ballooning if there is subsinusoidal collagen deposition. (Haematoxylin-eosin. Original magnification × 400)

(Fig. 1b).[2,8] Mallory's hyaline is typically sparse or absent. The fibrosis begins as fine, subsinusoidal deposition in the perivenular areas, later progressing in some patients as portal fibrosis, portal-central linkage and cirrhosis.

Grading and staging

Brunt *et al*. have suggested a grading and staging system for the analysis of steatohepatitis, addressing concerns that the use of standard schemas designed for chronic viral hepatitis concentrate on portal fibrosis rather than perivenular fibrosis, where the disease begins.[23] It should be noted that this is a proposal only and further validation studies are required. Despite this, it provides a useful framework to consider the range of lesions seen, but at this stage formal grading and staging are generally only performed for patients under study.

MANAGEMENT

At present the treatment options for NAFLD and NASH may seem limited. In most cases, treatment aims to achieve gradual weight loss of around 10% of body weight over 6 months and to sustain this. We have found that dietician review, initially weekly and then monthly after three months, is vital to achieve compliance and a lasting result. Exercise should also be part of the treatment regimen, since it appears to improve visceral adiposity and weight maintenance.[24] As an example, despite massive subcutaneous adipose tissue, sumo wrestlers do not have visceral adipose deposition or dyslipidaemia whilst training.[25] However, it does develop when training ceases. Other factors common in patients with the metabolic syndrome (hyperlipidaemia, hypertension and diabetes) need to be treated. Individuals with NAFLD and insulin resistance have a high rate of cardiovascular disease and this is one of the major reasons that these other risk factors need to be addressed.

There has been recent interest in drug treatment of NASH, but only pilot studies have been reported. Thiazolidinediones and metformin directed at insulin resistance, antioxidants such as vitamin E directed at oxidative stress, as well as gemfibrozil are some of the pharmacologic approaches that have shown some potential. It is stressed that the use of these agents is considered experimental and larger, controlled trials are needed before these therapies can be recommended.

Bariatric surgical intervention has a role in the morbidly obese patient and can assist sustained weight loss[17] but can have significant complications. Liver transplantation has a role in end-stage liver disease with decompensated cirrhosis. However these patients often have other manifestations of the metabolic syndrome, particularly cardiac disease, and are unable to tolerate the procedure.

SUMMARY

NAFLD is increasing in prevalence in association with the epidemic of obesity and type 2 diabetes. Hepatic steatosis alone is a benign process, but in the presence of excessive oxidative stress there is hepatocyte injury (ballooning and cell death), inflammation and the development of fibrosis. The oxidative stress may be intrinsic in primary NASH, or may be because of a second disease or process such as chronic viral hepatitis. A proportion of patients with NASH progress to cirrhosis, but this progression may be reduced with weight loss and exercise, or the removal of any offending aetiological factor. Future research aims to find non-invasive tests to identify the subgroup of patients with NASH who are at risk of progressive fibrosis, and explore new ways of treating and reversing the disease.

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