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Review

Non-alcoholic steatohepatitis (NASH):

A disease of emerging identity and importance

Oliver F. W. James and Christopher P Day
Centre for Liver Research, University of Newcastle upon Tyne, UK

ALTHOUGH its histological features had long been recognized (1). the term non-alcoholic steatohepatitis (NASH) was first used by Ludwig et al. as recently as 1980 (2). Although it is commonly encountered in hepatology outpatient (office) practice (3). surprisingly little attention has been paid to NASH. It will be the purpose of this review to examine the clinical and pathological features of NASH. to discuss its possible pathogenesis. and in the light of these to suggest possible management strategies.

Ludwig et al. described "the pathological and clinical features of non-alcoholic disease of the liver associated with the pathological features most commonly seen in alcoholic liver disease itself". This initial description remains appropriate since non-alcoholic. but alcoholic-like. liver disease ranges from simple steatosis through steatohepatitis and fibrosis to cirrhosis with fat. It may also be speculated that some causes of cryptogenic (non-fatty) cirrhosis originally arose through the NASH sequence and subsequently lost the fat (4). We suggest that the above spectrum. of which NASH is the central and most important entity, may be regarded as an acquired metabolic disease of the liver. resulting in the deposition of triglyceride within hepatocytes. in which progression to necro-inflammation. fibrosis and cirrhosis may occur.

Clinical Features

The perception of the clinical features of NASH may be changing. The consensus of most clinico-pathological studies of NASH has been that about 75% patients are female, almost all (69-l00%)) are obese. and about one-third have diabetes mellitus (usually non-insulin dependent diabetes (NIDDM)) (2,5-15). Many studies derived from liver pathology give few clinical details. but those that do give details suggest that most patients are asymptomatic. although mention is made of non-specific fatigue and weakness. and Powell et al. described right-sided abdominal pain upon enquiry in 18 of 42 patients (9). Table l summarizes nine studies. comprising 299 patients. Apart from liver enlargement, detectable in many of these patients. no other typical clinical signs develop until the conventional signs of cirrhosis and its complications. This "older wisdom" of the clinical picture of NASH has recently shifted and extended. In a study of unselected clinical practice-as opposed to a retrospective histological series. of "at risk" groups of patients. for example obese or diabetic individuals-Bacon et al. found that 53% of 33 patients were male and only 39%, were 10% over ideal body weight (13). A similar proportion of a recent Australian series. 26 out of 51 (52%). were also male (15). Almost all these patients were referred for investigation of abnormal liver function tests (LFTs). usually found incidentally. for example in connection with an application for life insurance. Systematic enquiry in both these series revealed that around half had symptoms which could be attributable to liver disease: persistent right upper abdominal discomfort and/or systemic systems of persistent fatigue or malaise.

In our own series of 40 patients. selected because of simple fatty change (no fibrosis or steatohepatitis) on liver biopsy. in whom alcohol had been rigorously excluded. the vast majority had been referred because of incidental finding of abnormal LFTs. Thirty percent of these were obese. $^{10\%}$ were diabetic. and none had marked symptoms of liver disease (14). We suggest that it is useful to include such patients in a review of NASH, since they must form part of the spectrum of the disease.

Causal Relationships in NASH

Obesity

While we have indicated that NASH should no longer be considered solely in the context of obesity. this is. nonetheless. the most consistently associated causal factor. In a thorough literature search of 41 papers

TABLE I

A. Clinical pathological series of NASH based upon histopathology. and B. Series extending the clinical picture of NASH

Reference	“	Mean age (years)	Female ("/”)	Obesity ("/”)	Diabetes/ elevated glucose (“/”)	Hyper. lipidemia	No symptoms of liver disease	Increased fibrosis cirrhosis
A								
Ludwig et al.(1980)(2)	20	54	65	90	50	67	na	IS
Adler & Schaffner(l979)(51	29	46	76	l00	2	48	na	47
Itoh et al.1l987)(6)	16	52	75	100	5	63	na	19
Diehi et al. (19881(7)	'9	52	81	71	55	20	77	39
Lee(l989) 18)	49	53	78	69	51	n/a	(00	34
Powell et al. (19901(9)	42	49	83	95	36	81	48	50
Laurin et al.(1996)(lO)	40	48	72.5	70	27.5	n/a	na	n a
Pinto et al. (1996(111)	32	49	75	47	34	28	94	
Hilden et al (19731(121	32	53	53	n/a	n/a	na	na	n a
	299	50	73	84	32	4Y	8))	
B								
Bacon et al. (19941)131	33	47	42	39	21	2!	64	39
Teli et al. (19951(141	40	57	45	30	10	23	lO0	(2.5".
George et al.(1998)(15)	51	47	49	n/a	n/a	n/a	na	

published before 1984. reporting on 1515 morbidly obese patients. Andersen & Gluud reported (unsurprisingly) excess fat in $_{80\%,}$ "parenchymal necrosis" in *5-63%.* fibrosis in *29%* and cirrhosis in 3% (16). There are relatively few more modern studies which have examined the frequency and severity of liver disease in populations of obese individuals. At post-mortem in non-alcoholic individuals (in Canada). 7% non-obese. non-diabetic individuals showed moderate steatosis and 2.7% steato hepatitis. Among markedly obese patients. 29% showed marked steatosis. and 19.5% had steatohepatitis-the likelihood of steatohepatitis increasing with degree of steatosis and obesity (17). For any degree of obesity, men and women were equally likely to have steatosis. steatohepatitis or fibrosis. In a cross-sectional study of liver histology in 50 unselected. obese (21-130% above ideal body weight) subjects admitted to hospital for weight reduction. Braillon et al. found 10% had normal livers, 48% fatty liver alone. 26% steatohepatitis, 8% fibrosis and 8% cirrhosis (18). These French authors also suggested an additive re-lationship between obesity and alcohol in respect of more fibrosis/cirrhosis.

NIDDM and hyperlipidaemia

Perhaps not surprisingly in view of its link with obesity NIDDM is present in about one-third of patients in the "classic" NASH clinical series (Table I) although in only $^{21\%}$ of Bacon's series (13). In the Canadian study, a history of NIDDM was associated with a 2.6-fold increase in the prevalence of steatohepatitis and fibrosis/cirrhosis. independent of the degree of fatty change or obesity (17). Wanless et al. have speculated that this is probably related to chronically elevated insulin levels rather than hvperglycaemia. since hyperinsulinaemia itself switches off normal hepatic acid β-oxidation (19). In support. NASH histology has been described in patients placed on peritoneal infusions of insulin (19). Similarly. where it has been sought. hyperlipidaemia is present in 20-8l%) patients (Table 1). Occasionally, either NIDDM or hyperlipidaemia is mentioned in the absence of obesity.

Weight-reducing surgery/bacterial contamination of small bowel

Jejuno-ileal bypass (JIB), once a popular treatment for severe obesity, has now been almost abandoned. largely because of the frequency of severe NASH followed by hepatocellular failure in such patients. Up to 40% of patients developed deterioration of LFTs following JIB and hepatocellular failure associated with severe NASH. not always resolved by surgical correction. developed in up to 67 it of patients (20.21). Severe NASH and hepatic failure are described far more rarely following biliopancreatic diversion. gastroplasty or itastric bypass for morbid obesity (22). There are two clues as to a possible causal factor for the development of severe NASH following JIB. First. NASH may be prevented or reversed in some patients following JIB by the use of metronidazole (23). Second. patients with bacterial contamination of the small bowel (BCSB) associated with duodenal or jejunal diverticular have been described with steatohepatitis and hyaline (24). We have three patients with BCSB in whom persistent moderate elevation of liver enzymes returned to normal after antibiotic treatment . A fourth patient was found to have "cryptogenic" cirrhosis. These reports strongly suggest a role for endotoxin in the pathogenesis of NASH (see below).

Medications

A number of drugs have been incriminated as being possibly associated with NASH. These include amiodarone and perhexiline maleate. These drugs are known to act as inhibitors of mitochondrial β oxidation and are, therefore. more readily associated with microvesicular steatosis (25,26). Nifedipine. diltiazem. stilboestrol. and tamoxifen have also been associated with more or less well-documented case reports. The field is well reviewed by Farrell (27). True histological and clinical NASH attributed to medications alone in the absence of either evidence of marked microvasicular steatosis or other clinical risk factors for NASH (obesity or NIDDM) is probably extraordinarily rare. Of other xenobiotics, Cotrim et al. have described a high occurrence of asymptomatic NASH (on liver biopsy) in workers chronically exposed to high atmospheric concentrations of several petrochemicals.' LFTs and macrovasicular steatosis improved in those removed from the environment (28).

Adolescent NASH

NASH has been described in a number of obese children around the age of puberty (29.30). As with adults. persistent moderate elevation of liver enshrines is common. Around half of these children complain of abdominal pain. Symptoms and blood tests did not correlate with the degree of steatosis. fibrosis or inflammation.

Clinical Course

No major prospective longitudinal clinical studies of NASH have been carried out. From existing case series we can conclude the following: in patients with fatty liver alone (little or no fibrosis or steatohepatitis) prognosis is excellent. No significant clinical or histological deterioration occurred in our own series of 40 patients with pure non-alcoholic fatty liver over a median 11-year follow-up (14).

Among the nine series of patients with NASH detailed in Table IA. l5-50% had histological evidence of significant fibrosis or cirrhosis. In these 299 patients. eight deaths from liver failure. two further non-fatal cases of liver failure and a transplantation for liver failure (total 11=3.1%) are described. It should be noted that almost all these studies were retrospective. Cross-sectional and originating from histological rather than clinical findings. Propst et al. have briefly reported a $^{67\%}$ 5-year survival and 59%; 10-year survival in 30 patients with NASH against 38%and 15%. respectively. in 65 patients with alcoholic steatohepatitis (31). No details as to the cause of death in the NASH patients were available. Among the two recent case series of Bacon et al. (13) and Powell et al. (9) describing (in Bacon's series) a higher proportion of men with incidental findings of persistently abnormal LFTs. histological progression was “slow". Only one of 42 patients in the Powell series (median follow-up 4.5 years) died of liver disease: no others showed significant clinical deterioration.

Until longitudinal studies are carried out. further conclusions will be speculative. At present. we would suggest that among non-obese or mildly obese. non-NIDDM patients the risk of progression of NASH to cirrhosis and its complications appears low. Among obese or morbidly obese individuals, and particularly those with NIDDM. the risk of progression either to severe NASH with liver failure or ultimately to cryptogenic cirrhosis is significant-possibly a life-time risk of around 5%. This risk appears proportional to the severity of histological change seen on

liver biopsy. presumably the lower the amount of fibrosis and steatohepatitis seen at histology the lower the risk. Very recently. George et al. have suggested that in a predominantly male group of patients with a high population risk of genetic haemochromatosis. increased liver iron staining and the presence of one copy of the haemochromatosis mutation C282Y was associated with a greater severity of fibrosis (15). At present. the exact significance of this finding in relation to disease progression is unknown.

Pathology

The range of liver pathology associated with non-alcoholic fatty liver is shown in Table 2. The pathology of NASH is well described in many of the publications already cited (2.5-8) and will not be fully described here. We would emphasize two ideas:

1. All 'stages' of NASH from pure fatty liver to end-stage cirrhosis may be indistinguishable histologically from alcohol-induced liver disease.
2. In any individual case no predictable correlation exists between symptoms (or lack of them). abnormality of LFTs (notably transaminases and gamma GT). and severity of histological lesions.
   Finally, we have included the histological feature of
   "fat alone" as part of the spectrum of NASH pathology. since we believe that it represents one end of a histopathological continuum.

Investigation

The diagnosis of NASH. regardless of severity rests upon three features. all of which must be present.

TABLE 2

NASH pathology

Stage	Pattern. features	Score
Fat alone	Macrovesicular	l.<33% hepatocytes
	Microvesicular	contain fat
	Mixed	2. 33-66%
		3.66%+
Steatohepatitis	Intra-acinar inflammation	Mav be graded 0-3
	Ballooning hepatocytes	May be graded 0-3
	Mallory bodies	May be graded 0-3
	Liver cell necrosis	May be graded 0-3
	(may include PASD-positive macrophages	
Fibrosis	Pericellular	May be graded 0-3
	Perivenular	May be graded 0-3
	Cirrhosis	

These are:

1. Histopathological features, of which the presence of fat and of alcohol-like liver damage are essential.
2. Rigorous exclusion of alcohol as a cause for the disease.
3. Appropriate investigations to exclude other forms of chronic liver disease.

Liver enzymes. notably transaminases. are usually persistently raised (24 times), although the level of elevation bears no relation to the underlying severity of the disease. To help distinguish between NASH and alcoholic liver disease, the ratio of alanine aminotransferase (ALT) to aspartate aminotransferase (AST) is almost always greater than 1 in NASH (where ALT exceeds AST) and almost always less than 1 in alcoholic liver disease (where AST is usually greater than ALT) (32). Exclusion of other possible causes of chronic liver disease by full hepatitis C and B serology iron studies. and haemochromatosis genetics should be carried out. In patients with suspected NASH. diabetic status should be checked. together with fasting lipids. It is perhaps worth noting that in four of our patients there was a positive SMA or *AMA* in the serum but no other clinical. immunological or histological features of autoimmune liver disease. Four of Bacon's patients were also AMA positive with no other evidence of autoimmune disease.

It may be argued that in asymptomatic patients, particularly with one or more known risk factors for NASH-obesity, NIDDM, or hyperlipidaemia-ultrasound diagnosis of fatty liver is all that is required without histological confirmation. We would strongly urge that this is not the case. First. the predictive value of a diagnosis of NASH without liver biopsy is perhaps as surprisingly low as 56% (33). Second. ultrasound is not always adequately sensitive (34), or specific in detection of fatty liver. Furthermore. detection of degrees of fibrosis and inflammation by ultrasound or even by computerized tomography or nuclear magnetic resonance in the presence of fat is poor in precisely the circumstances where this is important (35). Finally. since advanced NASH carries significant if unmeasured risks of development of cirrhosis and liver failure whereas, as we have indicated. pure fatty liver alone does not, then in order to advise on prognosis. the necessity of follow-up. or treatment. histology is necessary.

Management

Management of the NASH spectrum depends on both the histological severity and the presence or absence of underlying or associated conditions. In patients with pure fatty change in the liver. we suggest that no treatment is indicated beyond a recommendation to lose weight gradually if obesity is present. Patients with features of mild or moderate steatohepatitis with or with-out fibrosis will usually have underlying causally related conditions. At least in patients with moderate obesity there is evidence in both adults *(36.37)* and children (38) that sensible weight reduction leads to improvement not only of liver blood tests but also of histology and symptoms of abdominal pain and fatigue malaise. In patients with NIDDM or hyperlipidaemia weight reduction will of itself. improve that condition. although at present there is no evidence that treatment of NIDDNI or hyperlipidaemia associated with NASH is itself beneficial to the liver condition. For example. a trial of clofibrate had no effect on any parameter of NASH (10). In patients in whom NASH may be attributable to a xenobiotic. cessation or removal is obviously necessary. There is a suggestion that Ursodeoxycholic acid (UDCA) may possibly benefit NASH patients. irrespective of underlying associated conditions. One trial has demonstrated that VDCA improved enzymes and steatosis on biopsy but there was no demonstrable change in grade of liver inflammation or fibrosis (10). A case report from the same centre also reported normalization of LFTs on two occasions and improvement of liver histology with UDCA (39). A recent small uncontrolled study has suggested that a-tocopherol might improve NASH. possibly by reducing the severity of oxidative stress (40). Several authors advise severe restriction of alcohol consumption among NASH patients: this seems sensible.

In patients with morbid obesity and signs of severe NASH with liver failure. weight reduction is paramount. However. sudden marked weight reduction. presumably accompanied by great fluxes in free fatty acids (FFAs). may lead to fatal hepatic failure (41). Following weight-reducing surgery in these patients. prophylactic treatment with metronidazole would seem sensible if any progressive abnormality of LFTs develops (23). Liver transplantation has been successfully carried out in patients developing liver failure resulting from NASH following JIB (42). Recently recurrence of cirrhotic liver failure resulting from NASH has been recorded in three patients following liver transplantation for this condition (42). In no case had revision of the JIB been carried out.

Pathogenesis

Recent experimental evidence in man and in animals now offers us a chance to begin to understand the pathogenesis of NASH. Furthermore. we may also begin to answer questions concerning both the connection between simple macrovesicular steatosis and the development of steatonecrosis and fibrosis. and the histological Similarity between NASH and alcoholic steatohepatitis.

Oxidative stress and lipid peroxidation

Macrovesicular steatosis. characteristic of NASH. arises from one or more of: increased mobilization and availability of FFAs. increased hepatic synthesis FFA's, increased esterification of FFAs into triglyceride. and decreased export of triglyceride from the liver. Microvesicular steatosis is associated with impaired mitochondrial beta oxidation. Recently. Pessavre's group have demonstrated that acute or chronic fat deposition in the liver. regardless of cause. is associated with lipid peroxidation (43). Furthermore. in this experimental mouse model the degree of lipid peroxidation increased with the severity of steatosis.

One of the end products of peroxidation is malondialdehyde. which activates hepatic stellate cells stimulating collagen production. and hence fibrosis. It may also cross-link cytokeratins to form Mallory bodies. A further product of lipid peroxidation 4-hydroxynonenal. is strongly chemoattractant for neutrophils. Malondialdehyde may also contribute to inflammation by activating NF-KB. which regulates the expression of pro-inflammatory cytokines. including tumor necrosis factor a (TNFα) and IL-8 (44). Increasing evidence has implicated a role for lipid peroxidation in the pathogenesis of alcoholic steatohepatitis which may therefore explain their common histological features.

Whereas in alcoholic steatohepatitis there are several potential causal factors for oxidative stress required to initiate lipid peroxidation. these have been less clear for NASH. Two candidate sources of oxidative stress have emerged. The risk factors for steatohepatitis fibrosis in NASH-rapid weight loss or NIDDM-lead to increased concentrations of FFAs within the liver. If mitochondrial β-oxidation is saturated. paroxysmal β-oxidation will provide a source of oxidative stress by generating hydrogen peroxide. This is converted to highly reactive hydroxyl radicals in the presence of free iron (45). In this connection the recent observation by George et al. that there was overrepresentation of the C282Y mutation in the haemochromatosis gene *HFE.* and particularly some excess stainable liver iron among a series of patients with NASH, is germane (15).

A second source of oxidative stress in NASH. common to alcoholic steatohepatitis has been suggested by Farrell's group, who used a diet deficient in methionine-choline in a rat model of steatohepatitis to show a marked increase in cytochrome P450 CYP2El (46). This is induced not only by ethanol but also by FFAs and ketones, which presumably explains why it is upregulated in diabetes and obesity, where it is capable of generating excess reactive oxygen species (ROS) during metabolism of endogenous ketones and dietary constituents as well as ethanol (47).

Endotoxin-cytokine-mediated injury

The high incidence of severe NASH following JIB. and its partial prevention or reversal by metronidazole treatment suggest a role for portal endotoxaemia analogous to that seen in alcoholics due to increased gut permeability and impaired RE function. Recently Diehl's group have demonstrated that genetically obese-rodents are exquisitely sensitive to the effects of low doses of lipopolysaccharide (LPS), developing a severe NASH not seen in lean control animals (48). LPS injury is mediated through TNFα and. while TNFα levels are not increased in the obese rodents in Response to LPS, mRNA of interferon gamma (which sensitizes hepatocytes to TNFα toxicity) was overexpressed. whereas mRNA of interleukin 10 (which is inhibitory to TNFα effects) was reduced in this model. Furthermore. the phagocytic activity of Kupffer cells was reduced. potentially allowing systemic endotoxaemia with release of pro-inflammatory cytokines from extrahepatic sites. including adipose tissue. This peripheral source of cytokines may contribute to the pathogenesis of hepatic necroinflammation and fibrosis.

The attractions of the mechanisms outlined above are as follows: (i) they are not mutually exclusive; (ii) they are common to alcoholic and non-alcoholic steatohepatitis and fibrosis; and (iii) they offer an explanation for the lower susceptibility to progressive disease observed in NASH compared to alcoholic liver disease. Oxidative stress and/or endotoxaemia associated with continuing ethanol ~insult" may be more persistent and severe than that in simple obesity. hyperlipidaemia. or NIDDM where. although there is macrovasicular steatosis. there is relatively less stimulus to necroinflammation/fibrosis, either by lipid peroxidation or endotoxaemia. However. in NASH in cir-cumstances where these stimuli are more persistent, for example. post-JIB or in morbid obesity with NIDDM. progressive disease is more commonly seen.

Additionally. we may speculate that genetic factors may also play a part in susceptibility to NASH. as we are beginning to see for alcoholic liver disease. Thus. genetic variations in CYP2El activity. potentially responsible for greater production of ROS in susceptible individuals. and polymorphisms of the TNFa-promoter. both putative susceptibility loci for alcoholic liver disease (49.50), may be worthy of study in NASH. Finally understanding of the

pathogenic mechanisms involved will lead to the development of more rational and specific strategies for prevention and treatment of the more severe manifestations of NASH. as well as alcoholic liver disease.

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