

ORIGINAL ARTICLE

Non-alcoholic steatohepatitis: a common cause of progressive chronic liver injury?

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Aim: To investigate the natural history of patients with non-alcoholic steatohepatitis by means of a prospective histological study.

Methods: One thousand five hundred and seventy one patients underwent liver biopsy at the Western Infirmary in Glasgow during the 10 year period 1985 to 1994. All biopsies were reported by a single pathologist: 62 were confirmed as having non-alcoholic steatohepatitis and prospective follow up was conducted in 1999. Repeat liver biopsy was carried out where appropriate to assess disease progression.

Results: Initial biopsy scores for the 62 patients (20 men; mean age at biopsy, 52 years) showed a mean of 1.85, 1.39, and 0.5 for necroinflammation, fibrosis, and iron stores, respectively. Forty six were traceable and invited for review, and 26 attended (six men; mean age at initial biopsy, 49.9 years) at a mean of 8.7 years after the initial liver biopsy. No patients had symptoms or signs of chronic liver disease. Four patients had normal liver function tests, one had cirrhosis; the remaining 21 were invited to have a repeat biopsy. Seven patients agreed, a mean 8.2 years after the initial biopsy, and repeat biopsy scores showed no significant difference over this time period, with mean scores of 1.71 (initial score, 2.14), 1.43 (initial score, 0.71), and 0.14 (initial score, 0) for necroinflammation, fibrosis, and iron stores, respectively.

Conclusion: In this series of patients with non-alcoholic steatohepatitis, with a mean clinical follow up of 8.7 years, and a histological follow up of 8.2 years, there was no evidence of progressive chronic liver injury.

Non-alcoholic steatohepatitis was first described on liver biopsy in 1980.¹ The histological appearances resemble alcoholic liver disease, but have particularly been noted in overweight diabetic women who deny significant alcohol intake.^{2,3} There is debate over the definition of non-alcoholic steatohepatitis. Some studies include patients across the whole spectrum from simple steatosis (that is, with no inflammation) to steatohepatitis, fibrosis, and cirrhosis.^{4,5} Others have included only those patients whose biopsy demonstrates diffuse steatosis with at least mild parenchymal inflammation.⁶⁻⁹ The original definition was of alcohol-like liver disease in patients not consuming significant amounts of alcohol (taken as less than 20 g/day). A recently proposed diagnosis of non-alcoholic fatty liver disease clearly encompasses the whole spectrum within its classification.¹⁰ There remains the question of whether simple non-alcoholic steatosis should be included within the spectrum of non-alcoholic steatohepatitis, at least for prospective follow up and research purposes, because simple steatosis appears to represent the harmless end of the spectrum.¹¹

Non-alcoholic steatohepatitis was originally thought to be a benign condition without progression to chronic liver disease. The reported prevalence of non-alcoholic steatohepatitis has been increasing, particularly in the Western world, although this is at least in part because of the enhanced awareness of the condition and our ability to exclude other forms of liver disease.¹²⁻¹⁵ More recently, it has been reported that non-alcoholic steatohepatitis is a common cause of progressive chronic liver disease, including cirrhosis.^{10,16} Furthermore, it has been proposed that patients with cirrhosis at presentation, but lacking histological features or serological markers to explain the cause (cryptogenic cirrhosis), may have progressed from non-alcoholic steatohepatitis to a "burnt out" cirrhosis.¹⁷ Non-alcoholic steatohepatitis was originally thought to be a disease associated with diabetes mellitus and

obesity, but there have also been reports of its increasing incidence in thin non-diabetic men.^{18,19} However, the natural history of non-alcoholic steatohepatitis has not been well documented and the number of patients included in prospective studies remains small.

"More recently, it has been reported that non-alcoholic steatohepatitis is a common cause of progressive chronic liver disease, including cirrhosis"

In our study we aimed to investigate the natural history of patients with non-alcoholic steatohepatitis by means of a prospective histological study.

METHODS

A retrospective review of all liver biopsies performed at the Western Infirmary in Glasgow over the 10 year period 1985 to 1994 was carried out to determine the prevalence of non-alcoholic steatohepatitis. Patients with simple steatosis on biopsy were not included in our study. All had been reported by a single pathologist (RNM MacS). Case records were then consulted and a final diagnosis of non-alcoholic steatohepatitis was made on the basis of a combination of clinical, laboratory, and biopsy features.

Brunt *et al* proposed a new scoring system for non-alcoholic steatohepatitis in 1999.²⁰ This system assigns a necroinflammatory grade for inflammation and steatosis from 0 to 3 and a stage for fibrosis from 0 to 4. This scoring system is becoming more widely accepted and was used in our study. Repeat liver biopsies were obtained where indicated (see below) and the change in non-alcoholic steatohepatitis scores evaluated. The comparison of paired biopsies allowed assessment of the individual rate of progression of fibrosis (fibrosis units/year = difference in fibrosis stage between biopsies/interval in years

between biopsies). The median rate of progression of fibrosis and the median number of years to progress to the stage of cirrhosis (4/median fibrosis units/year) were calculated in a similar manner to that used for chronic hepatitis C.²¹

All biopsies were scored in a blind fashion by a second pathologist (KO). To facilitate further analysis an individual score (range, 0–4+) for iron stores²² was reported for each biopsy, although this had also been considered in determining the necroinflammatory score.

Patients

All the patients with non-alcoholic steatohepatitis who were alive in 1999 were invited back for clinical review. A proforma was completed for patients attending for review that included past medical history, social and drug history, and an assessment of alcohol consumption. Patients were not included if they were thought to have a regular alcohol intake of greater than 20 g/day; most were in fact consuming considerably less. They were also examined for stigmata of chronic liver disease, and a full liver screen was performed to exclude biochemical and serological markers of other forms of chronic liver disease. The haemochromatosis HFE genotype was analysed. Patients with clinical evidence of liver disease or abnormal liver function tests were invited to undergo a repeat liver biopsy. All biopsies were performed by Tru-cut needle under ultrasound guidance.

Statistics

Biopsy scores were compared using the Wilcoxon rank sum test. The study protocol was approved by the Western Infirmary ethics committee.

RESULTS

One thousand five hundred and seventy one patients underwent liver biopsy at the Western Infirmary in Glasgow during the 10 year period. On review of the histopathology reports by the first author (CE), 152 (9.7%) were identified as potentially having features of non-alcoholic steatohepatitis. After careful case record review, further information from the general practitioner, and a review of the liver biopsy slides, 62 (3.9%) were confirmed to have non-alcoholic steatohepatitis. Most of these patients had been referred for investigation of incidentally noted abnormal liver function tests.

The study population of 62 patients consisted of 42 women and the mean age at initial biopsy was 52 years. In only 46 cases was it possible to identify sufficient details to enable patient follow up. Problems included insufficient demographic information recorded in the pre-computerised days, patients having changed address and their general practitioner without this information being recorded, and the destruction of some case records from the 1980s at the Western Infirmary because of limitations on storage space.

Of the 46 patients, 33 were women and the mean age at initial biopsy was 50.9 years. Sixteen were diabetic, and three of these patients required insulin. Body mass index (BMI) was obtained for 32 of the 46 patients: 16 were obese (BMI > 30) and 14 were overweight (BMI > 25). Four patients had died (but on review of the records no death was thought to be attributable to liver disease), two were deemed unfit for recall by their general practitioner because of dementia or frailty, and three had moved outside the area: the remaining 37 were invited for review. Twenty six of these patients attended for follow up, two declined, and nine did not respond to three separate invitations to clinic appointments and declined telephone contact. Analysis of these 11 non-attending patients revealed that six continued to report to the hospital for management of their medical problems and in none of them were symptoms or signs of chronic liver disease documented in the case records.

Table 1 summarises the demographic data for the 26 patients who attended for review. No patient had symptoms or signs of chronic liver disease. The mean age at index biopsy was 49.9 years and at clinical review 58.6 years. Twenty were women, nine were diabetic, and of the 24 patients for whom we have accurate BMI data, 12 were obese and 10 were overweight. At the time of the index biopsy, one patient (number 22) had been on tamoxifen for breast cancer (stopped in 1995), which has been described to cause non-alcoholic steatohepatitis.²³ No other cause for chronic liver disease was found. Table 1 also shows the liver function tests at review. Serum albumin and bilirubin were normal in all patients. The remaining liver function tests were usually only mildly abnormal and were completely normal in four patients. One patient had cirrhosis on index biopsy and it was not felt appropriate to repeat the biopsy. The other 21 were invited to undergo a repeat liver biopsy and seven agreed (patient numbers 1–7).

Table 2 shows the index liver biopsy scores for all 62 patients in our non-alcoholic steatohepatitis study population: the 26 patients who attended for review appear to be a representative sample with respect to biopsy scores.

In table 3 the initial and repeat liver biopsy scores for the seven patients in our study are compared. There is no significant change in the three scores over a mean of 8.2 years. The median difference for necroinflammation was 0, for fibrosis it was +1, and for iron 0. The median rate of progression of fibrosis was 0.088 fibrosis units/year allowing a calculation of the median number of years to progress to cirrhosis in this population to be 45 years.

The HFE genotype was analysed in 25 of the 26 review patients. Five of our 25 patients were heterozygous for the C282Y mutation and one of them was a compound heterozygote for C282Y and H63D, similar to the reported background prevalence of 8–17% in our local population.^{24, 25} On liver biopsy, four of the heterozygotes had an initial iron score of 0 and one had a score of 1. Two underwent repeat biopsy, the iron score remaining at 0 in one, although the compound heterozygote iron score changed from 0 to 1 after 5.5 years of follow up.

DISCUSSION

Non-alcoholic steatohepatitis is an increasingly common condition in clinical practice, as are overweight people with minor abnormalities of their liver function tests. There is no consensus on how best to investigate and manage patients referred to the outpatient clinic with such abnormalities, or which patients should undergo a liver biopsy. Even with a biopsy confirmed diagnosis of non-alcoholic steatohepatitis the recommended course of management remains unclear. Our study reports data on 26 patients with a mean clinical follow up time of 8.7 years, and histological follow up on seven of them after a mean period of 8.2 years. Clinically there were no symptoms or signs of chronic liver disease, and the liver function tests remained only mildly abnormal. Repeat histological examination in seven patients showed no significant overall change in inflammatory score or fibrosis stage after a mean period of 8.2 years. However, the patients with the longest follow up showed a tendency for fibrosis to advance, but at a rate that would take 45 years to advance to cirrhosis and even longer to cause clinical illness.

There are three reports from 1989 to 1994 assessing the natural history of non-alcoholic steatohepatitis with repeat histology.^{6–8} All were retrospective studies with repeat histology available for a combined total of 26 patients after a mean follow up of only 3.9 years. One patient improved, in 13 there was no change, and 12 showed evidence of disease progression, with five progressing from fibrosis to cirrhosis. A fourth study assessed the natural history of simple non-alcoholic steatosis and concluded that it is a benign condition;¹¹ repeat histology was available for 12 patients at a mean of 11 years

Table 1 Demographics of 26 patients who attended for review; patients 1–7 underwent a repeat liver biopsy

Patient number	Sex	Age at review (years)	Length of follow up (years)	BMI	Diabetes mellitus	ALP (U/l)	AST (U/l)	ALT (U/l)	GGT (U/l)
1	F	57.3	14	30.2	No	367	48	63	185
2	M	42.5	11.9	28.1	No	197	31	50	15
3	F	66.5	11.4	32.5	Yes	400	71	81	177
4	M	52.8	7	37.2	Yes	262	25	47	158
5	F	62.4	6.4	41.3	Yes	275	46	42	49
6	F	68.4	6.0	28.2	No	191	27	23	71
7	M	52.8	5.5	29.3	No	232	21	30	93
8	F	74.7	13.4	25.9	Yes	202	55	42	86
9	F	55.1	13.2	35.7	No	312	60	77	105
10	F	58.6	12.7	30.0	Yes	251	15	15	27
11	M	66.8	11.3	27.0	Yes	331	34	85	151
12	F	67.3	10.5	30.5	No	278	61	50	78
13	F	52.3	10.1	30.0	Yes	173	26	26	94
14	F	56.9	9.5	32.0	No	239	28	15	60
15	F	41.8	9.2	32.1	No	209	21	28	123
16	F	72.2	8.7	23.8	No	374	57	50	283
17	F	56.7	8.1	33.4	Yes	229	17	10	32
18	F	52.3	8	24.9	No	107	66	81	156
19	M	45.8	7.8	–	No	154	34	69	157
20	F	64	7.3	31.2	No	414	27	15	65
21	M	74	7.2	26.2	Yes	326	21	28	219
22	F	47	6.2	28.7	No	229	28	39	35
23	F	67.1	6.1	28.6	No	117	22	17	19
24	F	42.7	5.4	–	No	241	22	36	56
25	F	68.4	5.1	33.4	No	252	28	44	127
26	F	56.7	4.9	30.1	No	232	78	138	67
Normal range						70–260	10–35	10–50	5–50
Mean	20 F	58.6	8.7	30.4	9 Yes	254	37	47	103

ALP, serum alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; BMI, body mass index; GGT, γ glutamyl transferase.

Table 2 Initial liver biopsy scores in our study population

	Necroinflammation	Fibrosis	Iron
Range	0–3	0–4	0–3
All patients n=62			
Median	2	1	0
Mean	1.85	1.39	0.5
Review patients n=26			
Median	2	1	0
Mean	1.96	1.04	0.27

after the index biopsy. Eleven patients had unchanged histology and in one patient there was progression to mild fibrosis 9.8 years after the index biopsy.

“The patients with the longest follow up showed a tendency for fibrosis to advance, but at a rate that would take 45 years to advance to cirrhosis and even longer to cause clinical illness”

The histological progression so far documented has been from non-fibrotic steatohepatitis to fibrosis or from fibrosis to cirrhosis. There has been no report of a patient progressing from simple steatosis or non-fibrotic steatohepatitis at index biopsy to cirrhosis. It is postulated that those patients with simple steatosis or steatohepatitis without fibrosis occupy the benign end of the spectrum, and that risk factors for progressive disease include obesity, diabetes mellitus, increased insulin resistance, systemic hypertension, age greater than 45, and an aspartate transaminase to alanine transaminase ratio greater than 1.^{9 26} Until the introduction of the Brunt scoring system there was no satisfactory scoring system for non-alcoholic steatohepatitis, and hence the histological assess-

ment in these three studies is arbitrary, making comparisons difficult. The paucity of data on the natural history of non-alcoholic steatohepatitis indicates the difficulty in conducting this form of study. Our single centre study from a large university hospital over a 10 year period of patient accrual has resulted in a relatively small cohort of patients for follow up. However, these patients remained well and showed only slow progression of liver disease, which may never become clinically relevant.

George *et al* reported that the haemochromatosis C282Y mutation in patients with non-alcoholic steatohepatitis was associated with an increase in iron load and was causally associated with ongoing chronic hepatic injury.²⁷ Our data do not support this association.

The underlying cause of hepatic inflammation and injury in non-alcoholic steatohepatitis remains unclear, but the roles of peripheral insulin resistance, oxidative stress, and mitochondrial abnormalities are being investigated.^{28–30} Other factors implicated include small bowel bacterial overgrowth, endotoxin, and tumour necrosis factor α .^{31–33} Although the natural history remains uncertain, studies have investigated the effect of weight reduction, good control of diabetes, and the use of ursodeoxycholic acid, *N*-acetyl cysteine, and metformin in treatment.^{34 35} Currently, no treatment has been shown to improve the natural history of this condition. Further multicentre studies with long term follow up will be required to find out which patients are at risk of disease progression, how quickly they progress, and whether there are any serum markers of progression. Only then will it be appropriate to assess possible therapeutic interventions.

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Table 3 Liver biopsy scores from the patients who underwent repeat biopsy

Patient number	Index biopsy			Repeat biopsy			
	NI	Fib	Iron	Interval (years)	NI	Fib	Iron
2	2	0	0	11.9	2	2	0
3	2	1	0	11.4	2	2	0
1	2	0	0	9	2	1	0
4	2	0	0	7	1	0	0
5	2	2	0	6.4	2	3	0
6	3	2	0	6	2	2	0
7	2	0	0	5.5	1	0	1
Mean	2.14	0.71	0	8.2	1.71	1.43	0.14

NI, necroinflammatory grade; Fib, fibrosis stage.

Take home messages

- In this series of patients with non-alcoholic steatohepatitis, with a mean clinical follow up of 8.7 years, and a histological follow up of 8.2 years, there was no evidence of progressive chronic liver injury
- The patients remained well and showed only slow progression of liver disease, which may never become clinically relevant
- Further multicentre studies with long term follow up are needed to identify those patients at risk of disease progression, how quickly they progress, and to define serum markers of progression; only then will it be appropriate to assess possible therapeutic interventions

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