CLINICAL AND HISTOLOGICAL FEATURES OF NON-ALCOHOLIC STEATOHEPATITIS IN IRANIAN PATIENTS

N. Ebrahimi Daryani, Sh. Mirmomen, H. Bahrami, B. Haghpanah and A. Nayerhabibi

Department of Gastroenterology, Imam Khomeini Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Abstract- Non-alcoholic steatohepatitis (NASH) is a disease of unknown origin characterized histologically by alcoholic-like liver injury in the absence of significant alcohol intake. This study was conducted to assess the clinical and pathological features of NASH patients in Iran. Patients with elevated liver transaminases, negative serologic markers of viral or autoimmune hepatitis and no findings in favour of metabolic liver disease were enrolled. A careful history was taken with special attention to alcohol intake and ultrasonography and liver biopsy were performed in those with no evidence of significant alcohol intake. A histology showing moderate to gross macrovesicular fatty change with inflammation (lobular or portal), with or without Mallory bodies, fibrosis, or cirrhosis, was considered diagnostic for NASH. Patients with mild steatosis were rechecked for the presence of hepatitis C virus (HCV) infection. Fifty-three patients who met the above criteria entered the study. Thirty-two patients (60.4%) were male and 21 (39.6%) were female with the mean age of 37.8±11.3 years. Twenty-six patients (55.3%) were overweight and 15 (31.9%) were obese. Forty patients (75.5%) had dyslipidemia and three patients (5.7%) were diabetic. Mean AST to ALT ratio was 0.95±0.52; 65.3% of patients had a ratio below than 1, and 95.9% were below of 2. Ultrasonography was abnormal in 32 (76.2%) patients. Liver biopsy showed mild steatosis in 35.7%, moderate steatosis in 53.6%, and severe forms in 10.7%. In 80.2% of patients, portal inflammation was present, and 15.1% had some degrees of fibrosis. The amount of increase in liver enzymes bore no relationship with the presence of fibrosis, portal inflammation, and degree of steatosis (P>0.05). The patients were somewhat younger than other studies, and most of them were male which might be due to the low rate of alcohol consumption in our country. Most of the patients had body mass index (BMI) higher than normal. Our findings show that NASH must not be considered a disease confined to high-risk groups only, and its impact might be larger than what is generally considered.

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Key Words: Nonalcoholic steatohepatitis, liver biopsy, fatty liver disease, steatosis, obesity

INTRODUCTION

Non-alcoholic steatohepatitis (NASH) is a disease of unknown origin characterized histologically by alcoholic-like liver injury in the absence of significant alcohol intake (1,2). NASH is considered as a type of chronic hepatitis and is a severe form of a spectrum called non-alcoholic fatty liver disease (NAFLD) (3). NAFLD has four histological stages: (1) fatty infiltration of the liver (2) fatty infiltration plus inflammation (3) fatty infiltration with ballooning degeneration (4) fatty infiltration with lesions similar to alcoholic hepatitis and sinusoidal fibrosis, polymorpho-nuclear infiltration with or without Mallory hyaline.

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Correspondence:
N. Ebrahimi Daryani, Department of Gastroenterology, Imam Khomeini Hospital, School of Medicine, Tehran University of Medical Sciences, Keshavarz Blwd, Tehran, Iran P.O. Box: 14515-1411
Tel: +98 21 6947985
Fax: +98 21 6490021
E-mail: Daryaniclinic@yahoo.com

NASH is the name given to the third and fourth stages (4,5).

The prevalence and clinical significance of NASH appears to be more than what is generally believed (6-9). Among patients who have had liver biopsies, NASH is seen in approximately 7 to 9 percent in Western countries (10,11). Ultrasonographic studies on normal population show a prevalence of 25 percents in the United States (5,12). The disease predominantly occurs between the ages of 40 and 60, (7,13) although there have been reports in children over the age of 10 (14,15).

Although the exact etiology of NASH remains unknown, it is frequently associated with disorders such as insulin resistance, obesity, type 2 diabetes mellitus, hyperlipidemia, protein-caloric malnutrition, and jejunoileal bypass surgery (5,7-10,16-19). It is important to consider that NASH can progress to cirrhosis and hepatic failure (7,8) further underscoring its importance as a potentially serious and life-threatening disease.

MATERIALS AND METHODS

Patient selection

The cohort of patients reviewed here were selected from all patients between 15 and 65, referred to Gastroenterology and Hepatology Clinic of Imam Khomeini Hospital, Tehran, Iran, from March 20, 1999 to November 21, 2001. Patients with elevated liver transaminases, negative serologic markers of viral or autoimmune hepatitis and no findings in favour of metabolic liver diseases were enrolled. A careful history was taken with special attention to alcohol intake and ultrasonography was performed in those with no evidence of significant alcohol intake. From eighty-six patients who had normal or increased echogenicity of the liver, an informed consent was sought for performing liver biopsy. Patients who did not consent to liver biopsy, or those on medications known to result in steatosis were excluded. Out of eighty-six, seventy-four patients were eligible for liver biopsy and 53 had a definite diagnosis of NASH.

Laboratory and pathological studies

Levels of aminotransferases, alkaline phosphatase, total bilirubin, serum cholesterol and triglycerides, fasting blood sugar and prothrombin time were measured using standard techniques. The definite diagnosis of NASH was based on a histology showing moderate to gross macrovesicular fatty change with inflammation (lobular or portal), with or without Mallory bodies, fibrosis, or cirrhosis. Also, all patients with pathologic diagnosis of mild steatosis were rechecked for hepatit C virus (HCV) infection, which was negative in all. A single radiologist performed all ultrasonographic studies and all pathologic studies were performed and reported by one pathologist. Overweight was defined as a BMI between 25 and 29.9 kg/m^2 , and obesity as body mass index (BMI) equal or above 30 kg/m^2. Ideal weight for height was calculated by Harnwi Method (20) (Men: 48.18 kg for 150 cm ± 1.1 kg per cm over/under 150 cm; Women: 45.45 kg for 150 cm ± 0.91 kg per cm over/under 150 cm). Dyslipidemia was defined according to guidelines of ATPIII (21). Thus, patients with one of the criteria of LDL-C >160, total cholesterol >200, triglycerides ≥ 150, or HDL-C < 40 were considered dyslipidemic. Risk factors for NASH, according to previous studies, included diabetes mellitus, hyperlipidemia, obesity, history of significant weight loss or weight gain, history of consumption of esterogens or androgens, and extensive abdominal surgery.

Statistical analysis

The results of quantitative variables are presented as mean± SD and those of qualitative variables as numbers and percentages. t-test was used to compare quantitative variables between subgroups of patients, and differences between categorical variables were analyzed by Chi Square. Logistic regression analysis was used to assess the effect of different factors on histological findings in liver biopsy specimens. A significance level of 0.05 was used.

RESULTS

Of the 5-31 patients whose diagnosis was confirmed by biopsy, 32 (60.4%) were male and 21 (39.6%) were female with the mean age of 37.8 ± 11.3 years. Mean weight of the patients was 83.8 ± 19 kg and mean BMI was 29.3 ± 4.7 kg/m^2. The mean BMI was significantly higher in men compared with women (30.7 ± 4.9 vs. 27.3 ± 3.5, $P<0.05$) (Table 1). Twenty-six patients (55.3%) were overweight and 15 (31.9%) were obese. Obesity was more common among men, and more women than men had normal BMI (Table 1). None of the patients had weights less than the ideal weight for their heights. On the average, the patients had weights 36.3 ± 20.5% (ranging from 0 to 125.2%) higher than the ideal weight and 94.3% of the patients had weights more than 10% higher than the ideal weight for their height (the mean ideal weight for height of the patients was 61.4 ± 9.6 kg). Six patients (11.3%) had a history of considerable weight loss and 12 patients (22.7%) reported an increase in weight during the last year. Eleven patients (20.8%) had a history of drug consumption for at least 2 months during the 6 months prior to the study. These drugs included NSAIDs (3 patients), esterogen (2 patients), levothyroxine (2 patients), tricyclic antidepressants (4 patients).

Three patients (5.7%) were diabetic. Forty patients (75.5%) had some form of dyslipidemia; in 65.2% serum cholesterol was high, in 61.4% hypertriglyceridemia was present, and both cholesterol and triglycerides were high in 67.9%. Five patients (9.5%) had none of the risk factors usually associated with NASH. The mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were 69.1 ± 38.9 IU/L and 56.8 ± 33.7 IU/L, respectively. Mean AST to ALT ratio was 0.95±0.52. This ratio was below 1 in 65.3% of patients and below 2 in 95.9%.

In 31 patients (58.5%) abnormal ultrasound findings were observed; 17% of all patients had increased liver size, and 50.9% had hyperechogenicity, indicating fatty liver.

Liver biopsy showed that steatosis was mild in 35.7%, moderate in 53.6%, and severe in 10.7%. Portal inflammation was present in 80.2% of patients and 15.1% had some degrees of fibrosis. The results of logistic regression analysis showed no relationship between the level of liver enzymes and fibrosis, portal inflammation, and steatosis.

Table 1. Anthropometric and biochemical characteristics of 53 patients with NASH

	Male	**Female**	**Total**
Number	**33**	**21**	53
Age (y)	**36.0±10.6**	**40.5±11.9**	37.8±11.3
Weight (kg)	**93.6±16.5**	**69.3±12.0**	83.8 ± 19
BMI (kg/m^2)	**30.7±4.9¤**	**27.3±3.5**	29.3±4.7
Obesity, n (%)	**13 (46.4)***	**2(10.5)**	15 (31.9)
Overweight, n (%)	**12 (47.9)***	**14(73.7)**	26(55.3)
Total cholesterol (mg /dL)	**229.6±73.5**	**223.5±62.5**	227.0±68.5
LDL-C (mg/ dL)	**139.5±42.3**	**123.0±43.3**	134.8±42.2
HDL-C (mg/ dL)	**47.6±16.1**	**4 3. 1± 13.6**	46.3±15.2
Triglycerides (mg/ dL)	**207±83.6**	**184±89.1**	197.3±85.8
FBS (mg/ dL)	**102.1±11.4**	**112.8±42.5**	106.5±28.1
ALT (U/ L)	**68.5-1:34.2**	**69.9±45.9**	69.1±38.9
AST (IU/ L)	**54.511126.4**	**60.1±42.9**	56.8±3 1.7
AST/ALT	0.93±0.48	0.98±0.59	0.95±0.52

*p<0.001 and ¤ p<0.05 compared to female patients

DISCUSSION

Nonalcoholic steatohepatitis is probably the third common reason for referral to specialists in gastroenterology and hepatology (22,23). Because of the low rate of alcohol consumption in our country, the prevalence might be even higher than in other countries.

Our patients were somewhat younger than those in previous studies (40-60 years old) (7,10,13). As mentioned above, this might be explained by higher rate of alcoholic liver disease in other countries. Also most of our patients were male (60.4%), while most of the previous series showed a female predominance, (8-10,17**)** and only a few had more male patients than females. One of the reasons for these differences might be the failure to rigorously rule out hepatitis C in some of the studies. We rechecked all patients with mild steatosis for hepatitis C infection. In the report mentioned before as showing a male preponderance (7), also hepatitis C was excluded with precision, and the patients had demographic characteristics different from those usually reported. Different sex composition of our patients might again be attributed to the higher alcohol consumption rate in other societies, which can cause a female predominance since usually men are more at risk of alcoholic liver disease.

The mean weight of the patients was higher than normal as in previous reports (9,10,16). Most patients had abnormally high BMI and 94.2% had weights more than 10% above their ideal body weights. 11.3% of the patients had a history of weight loss in the year before diagnosis, which was similar to other results (24,25).

Another difference between our results and other reports is the relatively low prevalence of diabetes. Although some reports have shown a prevalence of 2-5% for diabetes mellitus in this group (17,26) in most of them this prevalence is as high as 21-55% (10,7-9,16-19). An interesting fact is that some of our patients had none of the known risk factors for development of NASH, and NASH must be considered as an entity far from being confined to obese and diabetic patients. Liver enzyme levels in our patients were similar to previous reports (7). The mean AST to ALT ratio was less than 1 as expected, and in 95.9% this ratio was below 2. In alcoholic liver disease, this ratio is usually above two, averaging from 2.6 to 2.85 (24,27,28). We observed dyslipiderma in 75.5% of our patients. Others have reported similar prevalences (20-

80%) (7-10,18,19). The findings in ultrasonography, such as fatty infiltration, are usually nonspecific (29).

It is not usually advisable to make a diagnosis of NASH before liver biopsy. The possibility of making an erroneous diagnosis is higher in NASH as compared to alcoholic liver disease. In our study, although 74 patients were initially diagnosed as NASH, only 53 had hepatic steatosis. This figure is larger than the ones mentioned in other studies (30-33), which is probably due to precise patient selection in the present study, exclusion of cases with low transaminase levels, or positive markers for viral hepatitis. Factors affecting the pathogenesis of NASH are steatosis, inflammation, and fibrosis (34-38). The severity of steatosis was similar to other reports. Also, the majority of patients had portal inflammation. The findings on liver biopsy were not correlated to liver enzymes, thus the increase in liver enzymes does not seem a good estimate of the severity of liver disease. NASH can cause fibrosis and progress to cirrhosis. It has been shown that this progress is seen in 8-26% of patients (6,8,9,19). Hepatic fibrosis, Mallory hyaline, or ballooning degeneration are findings that indicate a higher likelihood of progression to cirrhosis. Altogether, these findings further underscore the importance of NASH and the need to diagnose it before it causes irreversible liver damage.

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