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BRIEF ARTICLE

Association between nonalcoholic fatty liver disease and acute ischemic stroke severity and outcome

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Abstract

AIM: To evaluate the association of nonalcoholic fatty liver disease (NAFLD) with acute ischemic stroke severity and in-hospital outcome.

METHODS: We prospectively studied all patients who were admitted in our Department with acute ischemic stroke between September 2010 and August 2012 (n = 415; 39.5% males, mean age 78.8 ± 6.6 years). The severity of stroke was assessed with the National Institutes of Health Stroke Scale (NIHSS) score at admission. NALFD was defined as serum alanine aminotransferase and/or aspartate aminotransferase levels above the upper limit of normal in the absence of other causes of elevated aminotransferases levels [chronic hepatitis B or C, drug toxicity, increased alcohol consumption (> 21 and > 14 drinks per week in men and women, respectively), cholestatic diseases or rhabdomyolysis]. The outcome was assessed with the modified Rankin scale (mRS) score at discharge and in-hospital mortality. Adverse outcome was defined as mRS score at discharge ⩾ 2. Dependency at discharge was defined as mRS score between 2 to 5.

RESULTS: NAFLD was present in 7.7% of the study population. Patients with NAFLD had lower serum high-density lipoprotein cholesterol and higher triglyceride levels than patients without NAFLD ($P < 0.05$ for both comparisons). Demographic data, the prevalence of other cardiovascular risk factors and the prevalence of established CVD did not differ between the two groups. At admission, the NIHSS score did not differ between patients with and without NAFLD (6.3 ± 6.4 and 8.8 ± 9.6, respectively; P = NS). At discharge, the mRS score did not differ between the two groups (1.9 ± 2.2 and 2.6 ± 2.2 in patients with and without NAFLD, respectively; P = NS). Rates of dependency at discharge were also similar in patients with and without NAFLD (36.8% and 55.0%, respectively; P = NS) as were the rates of adverse outcome (42.9% and 58.6%, respectively; P = NS). In-hospital mortality rates also did not differ between the 2 groups (8.0% and 7.0% in patients with and without NAFLD, respectively; P = NS).

CONCLUSION: The presence of NAFLD in patients admitted for acute ischemic stroke does not appear to be associated with more severe stroke or with worse in-hospital outcome.

Key words: Nonalcoholic fatty liver disease; Stroke; Outcome; Aminotransferases; γ-glutamyl transpeptidase; Cardiovascular disease; Type 2 diabetes mellitus; Obesity; Cardiovascular risk

Core tip: This is the first study that assessed the prevalence of nonalcoholic fatty liver disease (NAFLD) in patients admitted with acute ischemic stroke and the association between NAFLD and stroke severity and in-hospital outcome. NAFLD was present in 7.7% of the patients and was not associated with stroke severity or with in-hospital outcome (dependency at discharge and in-hospital mortality).

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of hepatic steatosis, proved histologically or by imaging, in the absence of increased alcohol consumption, pharmacotherapy or inherited disorders that can lead to secondary fat accumulation in the liver[1]. NAFLD is the commonest cause of elevated aminotransferases and ranges from isolated fatty deposition in the liver (steatosis) to liver steatosis with inflammation and fibrosis (nonalcoholic steatohepatitis, NASH)[1,2]. The prevalence of NAFLD in the general population ranges between 34%-46% whereas NASH is observed in approximately 12% of the general population[3-5].

Isolated hepatic steatosis and particularly NASH can progress to cirrhosis and are associated with increased incidence of hepatocellular cancer[1,5-8]. Moreover, patients with NAFLD appear to have increased cardiovascular risk compared with the general population[9,10]. Indeed, cardiovascular disease (CVD) is the leading cause of death in patients with NAFLD[9-12]. The frequent coexistence of NAFLD with established cardiovascular risk factors including obesity, type 2 diabetes mellitus (T2DM) and metabolic syndrome may in part explain the increased cardiovascular risk of these patients[9,10,13]. However, some studies indicated that NAFLD is independently associated with higher cardiovascular morbidity and mortality[11,12].

Ischemic stroke is the fourth leading cause of mortality in the developed world[14]. Studies in the general population suggested that patients with NAFLD have increased risk for stroke[9,10]. A recent case-control study in 103 patients with ischemic stroke and 200 controls also showed that elevated aminotransferase levels is associated with increased risk for ischemic stroke[15]. However, there is a paucity of data regarding the association between NAFLD and the severity and outcome of acute ischemic stroke. Accordingly, the aim of the present study was to determine the prevalence of NAFLD in patients admitted with acute ischemic stroke and to evaluate the association of NAFLD with stroke severity and in-hospital outcome.

MATERIALS AND METHODS

We prospectively studied all patients who were admitted in our Department with acute ischemic stroke between September 2010 and August 2012 (n = 415; 39.5% males, mean age 78.8 ± 6.6 years).

At admission, demographic data (age, sex), history of cardiovascular risk factors (hypertension, atrial fibrillation, smoking, alcohol consumption, family history of premature CVD, chronic kidney disease), history of concomitant CVD (coronary heart disease (CHD), previous stroke, congestive heart failure) and pharmacological treatment were recorded. Anthropometric parameters (weight, height, waist and hip circumference, waist to hip ratio) and systolic and diastolic blood pressure were also measured. The severity of stroke was assessed with the National Institutes of Health Stroke Scale (NIHSS) score at admission.

Routine laboratory investigations were performed the first day after admission after overnight fasting and included serum levels of glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), creatinine, uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (γ-GT), alkaline phosphatase (ALP), bilirubin (total, direct and indirect) and creatine kinase. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using Friedewald's formula[16]. Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease equation[17]. Chronic kidney disease was defined as estimated GFR < 60 mL/min per 1.73 m^2.

Nonalcoholic fatty liver disease was defined as serum ALT and/or AST levels above the upper limit of normal in the absence of other causes of elevated aminotransferases levels (chronic hepatitis B or C, drug toxicity, increased alcohol consumption (> 21 and > 14 drinks per week in men and women, respectively), cholestatic diseases or rhabdomyolysis)[1]. Liver ultrasonography was performed in all patients with elevated aminotransferases levels.

All patients underwent brain computed tomography at admission and a second brain computed tomography was performed if clinically indicated.

The outcome was assessed with the modified Rankin scale (mRS) score at discharge and in-hospital mortality. Adverse outcome was defined as mRS score at discharge ⩾ 2. Dependency at discharge was defined as mRS score between 2 to 5. The length of hospitalization was also recorded.

The study was approved by the Ethics Committee of the Medical School of the Aristotle University of Thessaloniki.

Statistical analysis

All data were analyzed with the statistical package SPSS

Table 1 Clinical characteristics of patients with nonalcoholic fatty liver disease and of those without nonalcoholic fatty liver disease

	Patients with NAFLD (n = 32)	Patients without NAFLD (n = 383)	P value
Age (yr)	77.4 ± 7.7	78.8 ± 6.4	NS
Males (%)	40	37.1	NS
Systolic blood pressure (mmHg)	150 ± 24	145 ± 24	NS
Diastolic blood pressure (mmHg)	84 ± 18	80 ± 13	NS
Hypertension	80%	82.5%	NS
Smoking (current/past)	17.4%/17.4%	10.9%/22.9%	NS
Package-years	17 ± 30	11 ± 31	NS
Type 2 diabetes mellitus	24%	31.8%	NS
Type 2 diabetes mellitus duration (yr)	3.9 ± 9.9	3.1 ± 6.7	NS
Atrial fibrillation	29.2%	38.9%	NS
Alcohol consumption (units/wk)	1.2 ± 2.5	2.3 ± 12.4	NS
Waist (cm)	107 ± 13	104 ± 12	NS
Waist/hip	1.03 ± 0.05	0.97 ± 0.07	NS
Body mass index (kg/m^2)	26.9 ± 3.5	27.3 ± 5.0	NS
Overweight/obese	47.1 %/17.6 %	40.7 %/24.3 %	NS
Family history of cardiovascular disease	31.8%	14.7%	NS
Coronary heart disease	37.5%	27.6%	NS
Previous ischemic stroke	21.7%	43.5%	NS
Chronic kidney disease	31.6%	35.1%	NS
Chronic heart failure	23.8%	23.2%	NS

NS: Not significant; NAFLD: Nonalcoholic fatty liver disease.

(version 17.0; SPSS, Chicago, IL, United States). Data are presented as percentages for categorical variables and as mean and standard deviation for continuous variables. Differences in categorical and continuous variables between groups were assessed with the χ^2 test and the independent samples t-test, respectively. Multiple logistic regression analysis was performed to identify independent predictors of dependency at discharge and of in-hospital mortality including factors with $P < 0.20$ by descriptive analysis. In all cases, a two-tailed $P < 0.05$ was considered significant.

RESULTS

NAFLD was present in 7.7% of the study population. Ultrasonography showed increased liver echogenicity in all these patients. Clinical characteristics of patients with NAFLD and patients without NAFLD are shown in Table 1. Demographic data, the prevalence of cardiovascular risk factors and the prevalence of established CVD did not differ between the two groups. Anthropometric characteristics and blood pressure at admission were also comparable in patients with and without NAFLD.

Laboratory characteristics of patients with NAFLD and patients without NAFLD are shown in Table 2. Patients with NAFLD had lower serum HDL-C and higher TG levels than patients without NAFLD ($P < 0.05$ for both comparisons). Serum LDL-C, glucose and uric acid levels and the estimated GFR did not differ between the two groups. Patients with NAFLD had higher serum ALT and AST levels than patients without NAFLD ($P < 0.001$ for both comparisons). Serum γ-GT levels were also higher in the former ($P < 0.05$). In contrast, serum ALP and bilirubin levels were comparable in the 2 groups.

At admission, the NIHSS score did not differ between patients with and without NAFLD (6.3 ± 6.4 and 8.8 ± 9.6, respectively; P = NS). The outcome of the 2 groups is shown in Table 3. The duration of hospitalization was comparable in patients with and without NAFLD (8.0 ± 5.1 and 6.7 ± 4.2 d, respectively; P = NS). The mRS score at discharge also did not differ between the two groups (1.9 ± 2.2 and 2.6 ± 2.2 in patients with and without NAFLD, respectively; P = NS). Rates of dependency at discharge were also similar in patients with and without NAFLD (36.8% and 55.0%, respectively; P = NS) as were the rates of adverse outcome (42.9% and 58.6%, respectively; P = NS). In-hospital mortality rates also did not differ between the 2 groups (8.0% and 7.0% in patients with and without NAFLD, respectively; P = NS).

In multiple logistic regression analysis, independent predictors of dependency at discharge were age (RR = 1.16, 95%CI: 1.05-1.28, $P < 0.005$), history of stroke (RR = 3.66, 95%CI: 1.25-10.71, $P < 0.05$) and the NIHSS score at admission (RR = 1.61, 95%CI: 1.34-1.92, $P < 0.001$). Independent predictors of in-hospital mortality were diastolic blood pressure at admission (RR = 1.06, 95%CI: 1.01-1.11, $P < 0.05$) and the NIHSS score at admission (RR = 1.17, 95%CI: 1.10-1.23, $P < 0.001$).

Among the 32 patients with NAFLD, 24 did not drink alcohol at all. When these 24 patients were compared with the rest of the study population (n = 391), similar results were obtained.

DISCUSSION

The present study suggests that NAFLD might not be

Table 2 Laboratory characteristics of patients with nonalcoholic fatty liver disease and of those without nonalcoholic fatty liver disease

	Patients with NAFLD (n = 32)	Patients without NAFLD (n = 383)	P value
Glucose (mg/dL)	125 ± 64	113 ± 46	NS
LDL-C (mg/dL)	112 ± 42	112 ± 40	NS
HDL-C (mg/dL)	39 ± 12	47 ± 15	<0.05
Triglycerides (mg/dL)	144 ± 65	119 ± 51	<0.05
Uric acid (mg/dL)	5.6 ± 1.8	5.7 ± 1.8	NS
eGFR (mL/min/1.73 m^2)	65 ± 19	69 ± 23	NS
Alanine aminotransferase (U/L)	35 ± 21	17 ± 13	<0.001
Aspartate aminotransferase (U/L)	56 ± 23	23 ± 17	<0.001
γ-glutamyl transpeptidase (U/L)	38 ± 29	24 ± 31	<0.05
Alkaline phosphatase (U/L)	71 ± 24	71 ± 32	NS
Total bilirubin (mg/dL)	0.83 ± 0.46	0.77 ± 0.48	NS
Direct bilirubin (mg/dL)	0.30 ± 0.19	0.28 ± 0.28	NS
Creatine kinase (U/L)	91 ± 40	119 ± 197	NS

LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; eGFR: Estimated glomerular filtration rate; NS: Not significant; NAFLD: Nonalcoholic fatty liver disease.

Table 3 Severity of stroke and outcome of patients of patients with nonalcoholic fatty liver disease and of those without nonalcoholic fatty liver disease

	Patients with NAFLD (n = 32)	Patients without NAFLD (n = 383)	P value
National Institutes of Health Stroke Scale score at admission	6.3 ± 6.4	8.8 ± 9.6	NS
Duration of hospitalization (d)	8.0 ± 5.1	6.7 ± 4.2	NS
Modified Rankin scale score at discharge	1.9 ± 2.2	2.6 ± 2.2	NS
Dependency at discharge	36.8%	55%	NS
Adverse outcome	42.9%	58.6%	NS
In-hospital mortality	8%	7%	NS

NS: Not significant; NAFLD: Nonalcoholic fatty liver disease.

associated with more severe stroke and that NAFLD does not appear to predict a worse in-hospital outcome in patients admitted with acute ischemic stroke.

The prevalence of NAFLD in patients with acute ischemic stroke in our study was 7.7%. To the best of our knowledge, there are no data regarding the prevalence of NAFLD or NASH in this population. The prevalence of NAFLD in the general population ranges between 34%-46%[3-5]. Since T2DM and obesity are associated with increased risk for both NAFLD and stroke, it might have been expected to find a higher prevalence of NAFLD in patients with acute stroke than in the general population. However, the diagnosis of NAFLD in the general population is primarily based on identification of hepatic steatosis with imaging[3,5]. In contrast, in the present study we defined NAFLD as the presence of elevated aminotransferases levels in the absence of other causes of chronic liver disease. It has been reported that less than one third of patients with NAFLD have elevated aminotransferases levels[3,5,18]. Therefore, the different definition of NAFLD might have contributed to the lower prevalence of NAFLD in our study.

We did not find any correlation between the presence of NAFLD and the severity of stroke at admission as assessed with the NIHSS. This is the first study that evaluated the association. A possible explanation for this finding is that patients with NAFLD and those without NAFLD had similar prevalence of CVD risk factors, except for the lower serum HDL-C and higher TG levels in the former. However, the association between these lipids and stroke severity has been inconsistent in epidemiological studies[19]. On the other hand, it is unclear whether NAFLD independently increases CVD risk or the higher incidence of cardiovascular events in this population is due to the increased prevalence of established CVD risk factors, particularly T2DM and obesity[9,10,20]. Some studies in the general population and in patients with T2DM suggested that NAFLD increases the risk for CVD even after adjusting for other CVD risk factors[15,21,22]. Moreover, NAFLD is independently associated with increased carotid intima-media thickness, a well-established marker of subclinical atherosclerosis[23-25]. Our results suggest that NAFLD might not be independently associated with greater stroke severity but larger studies are needed to resolve this clinically important and controversial issue.

Another important finding of the present study is that the presence of NAFLD in patients with acute

ischemic stroke does not appear to be associated with worse functional outcome at discharge. An earlier study suggested that NAFLD is associated with increased incidence of CHD but it does not predict the clinical outcome of patients with established CHD[26]. In patients with acute ischemic stroke, T2DM appears to be associated with worse functional outcome[27,28] whereas obesity is not[29]. Nevertheless, neither T2DM nor obesity was more frequent in patients with NAFLD in our study. There are no studies that evaluated the association between NAFLD and functional outcome in patients with acute ischemic stroke. Our findings suggest that this relationship might be week or absent but this remains to be confirmed or rejected in larger studies.

We did not find a difference in in-hospital mortality rates between patients with NAFLD and those without. In contrast, previous studies in the general population reported higher mortality rates in patients with NAFLD, with CVD being the leading cause of death[11,12]. There are no studies that evaluated the association between NAFLD and short- or long-term mortality in patients with acute ischemic stroke. However, a recent smaller study from India (n = 116 patients with acute ischemic stroke) reported that elevated ALT was associated with higher risk of death at 1 mo[30]. In the general population, some studies also found higher CVD mortality rates in patients with raised ALT[31] but others did not[32,33]. In the present study, mortality rates were higher in patients with NAFLD than in those without but this difference did not reach significance. It is possible that the small number of patients with NAFLD limited the statistical power of our study resulting in a type Ⅱ statistical error.

Apart from aminotransferases, serum γ-GT levels are also frequently elevated in patients with NAFLD. However, γ-GT is not a specific marker of NAFLD since it is also elevated in other hepatic (*e.g.*, cholestasis, alcohol- and drug-induced hepatitis) as well as extrahepatic diseases[1,8]. Some studies in the general population reported that γ-GT is an independent predictor of CVD events, including stroke[8,32-34]. However, when NAFLD was defined as the presence of elevated aminotransferases and/or γ-GT in the present study, again there was no association between NAFLD and stroke severity or outcome (data not shown).

In conclusion, the present study suggests that the presence of NAFLD in patients admitted for acute ischemic stroke might not be associated with more severe stroke or with worse in-hospital outcome. However, given the small number of patients with NAFLD in the present report and the lack of other studies evaluating this association, larger studies are needed to further evaluate the predictive value of NAFLD in this high-risk population.

COMMENTS

Background

Nonalcoholic fatty liver disease (NAFLD) is the commonest cause of elevated aminotransferases and ranges from isolated fatty deposition in the liver (steatosis) to liver steatosis with inflammation and fibrosis nonalcoholic steatohepatitis (NASH). The prevalence of NAFLD in the general population ranges between 34%-46% whereas NASH is observed in approximately 12% of the general population.

Innovations and breakthroughs

This is the first study that assessed the prevalence of NAFLD in patients admitted with acute ischemic stroke and the association between NAFLD and stroke severity and in-hospital outcome.

Applications

The presence of NAFLD in patients admitted for acute ischemic stroke does not appear to be associated with more severe stroke or with worse in-hospital outcome.

Peer review

This is an interesting article, it is well written.

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