ANNALS OF GASTROENTEROLOGY 2004, 17(3):230-233

Editorial

Non-Alcoholic steatohepatitis and primary hepatic carcinoma

E.V. Tsianos, D. Chirstodoulou

SUMMARY

Non-alcoholic fatty liver disease (NAFLD) has been recognized as the most frequent cause of chronic liver disease and comprises a spectrum of chronic liver diseases ranging from simple hepatic steatosis, to hepatic steatosis with non-specific hepatic inflammation, to non-alcoholic steatohepatitis (NASH) and finally cirrhosis. Few reports have been published so far about the incidence of primary hepatic carcinoma in patients with NAFLD and NASH. The importance of these findings remains to be defined, but one could speculate that hepatocellular carcinoma is part of the clinical spectrum of NAFLD and the metabolic derangement observed in patients with NAFLD may underlie the progression of liver disease to cirrhosis and hepatocellular carcinoma. Attempts should be made to interrupt the progression from simple fatty liver disease to steatohepatitis, fibrosis, cirrhosis and ultimately hepatocellular carcinoma. A behavioral approach, such as diet and exercise, to reduce the prevalence and the progression of obesity, diabetes and dyslipidemia, as well as the pharmacologic treatment of insulin resistance and the use of newer therapeutic agents of NASH, merit consideration in this clinical setting.

INTRODUCTION – EPIDEMIOLOGY

Non-alcoholic fatty liver disease (NAFLD) has been recognized as the most frequent cause of chronic liver disease and comprises a spectrum of chronic liver diseases ranging from simple hepatic steatosis, to hepatic steatosis with non-specific hepatic inflammation, to non-alcoholic steatohepatitis (NASH) and finally cirrhosis.[1,2] The prevalence of NAFL and NASH in the general population of the United States is estimated at 20% and 3% respectively and can be as high as 95% in high-risk subgroups with abnormal liver enzymes, type 2 diabetes mellitus, or morbid obesity. Prevalence of NASH has been reported in more than 50% in obese individuals with body mass index >30 and in patients with diabetes mellitus type II, but its prevalence in lean individuals can be as high as 35%.[3] NAFLD has been implicated in the pathogenesis of cryptogenic cirrhosis as a major cause; in fact 30-40% of cases of cryptogenic cirrhosis have been attributed to NAFLD, while 15-30% of patients with cryptogenic cirrhosis manifest histological findings compatible with NASH.[4]

Department of Internal Medicine and Hepato-Gastroenterology Unit, Medical School, University of Ioannina - Greece

Author for correspondence:

Dr Epameinondas V. Tsianos, Professor of Medicine, Department of Internal Medicine, and Hepato-Gastroenterology Unit, Medical School University of Ioannina – Greece, 45110, Ioannina, Greece, Tel: +30 26510 97501, Fax: +3026510 97016, e-mail: dchristo@cc.uoi.gr

NATURAL HISTORY AND CHARACTERISTICS OF NON-ALCOHOLIC FATTY LIVER DISEASE

The diagnosis of NAFLD is suspected in patients with elevated liver enzymes who do not consume significant amounts of alcohol (less than 210 g of alcohol in men and less than 120 g of alcohol in women per week, or even more rigorously less than 70 g of alcohol per week) and are obese, or have diabetes mellitus type 2 or hypertriglyredimia and in general have insulin-resistance and features of the metabolic syndrome. Other causes of chronic liver disease should be excluded, mainly viral, autoimmune hepatitis and hepatotoxic medications. Ultrasound examination is quite sensitive in the detection of NAFLD and the liver appears hyperechoic in most cases. Despite that, the specificity of ultrasound findings is less than 90% and the diagnosis is confirmed only by pathological evaluation of an adequate liver specimen, at least 2 cm long, which also has prognostic value. Liver histology of NAFLD is classified into 4 subtypes; type I is characterized by fatty degenaration, type II by fatty degeneration and lobular non-specific inflammation, type III by all the above and ballooning degeneration of hepa-

tocytes and type IV by all the above and fibrosis. Types III and IV characterize NASH and can progress to cirrhosis.

Five and ten year survival rates in patients with NASH is 67% and 59% respectively, but death is usually caused by cardiovascular complications of diabetes mellitus, obesity and hyperlipidemia. The rate of development of cirrhosis by NASH has been reported to be higher than that by chronic hepatitis C (20% versus 15% in 20 years).[1,5] In a recent study, 25% of patients with NASH progressed to cirrhosis and 11% died of liver-related causes.[3]

FACTORS ASSOCIATED WITH NON-ALCOHOLIC FATTY LIVER DISEASE AND HEPATOCELLULAR CARCINOMA

Angulo et al have proposed simple markers for the prediction of worsening liver histology in NASH. Independent predictors of liver fibrosis in patients with non-alcoholic steatohepatitis were age >40 years old, increased BMI index, presence of type II diabetes mellitus, hypertriglyceridemia, ALT >100 IU/L (normal values <40), AST/ALT ratio >1 and increased levels of IgA immunoglobulins in serum.[1,6]

In general, most cases of hepatocellular carcinoma are diagnosed in patients ho have had cirrhosis for many years. However it is not clear whether the neoplastic process begins during cirrhosis or starts at earlier stages of liver disease. If hepatocellular carcinoma begins during cirrhosis, then it is reasonable to speculate that hepatic insulin resistance might be involved, because advanced liver disease is generally associated with insulin resistance and the association between cirrhosis and diabetes is particularly strong in obese individuals.[7]

An experimental controlled study in genetically obese, leptin-deficient ob/ob mice, which are models of NAFLD, found, by comparing parameters of proliferation and apoptosis, that hepatic hyperplasia was evident at the earliest stage of NAFLD in ob/ob mice, which supports the concept that obesity-related metabolic abnormalities, rather than cirrhosis, initiate the hepatic neoplastic process during obesity.[8]

In cryptogenic cirrhosis, an overall prevalence of 6.9% of hepatocellular carcinoma was founds;[2,5] lower than the prevalence of hepatocellular carcinoma arising in cirrhosis related to alcohol or viral hepatitis, but higher than that for hepatocellular carcinoma arising in cirrhosis related to primary biliary cirrhosis. An univariate analysis showed that patients with cryptogenic cirrhosis and hepatocellular carcinoma were more likely to have type 2 diabetes mellitus, hypercholesterolemia, hypertriglyceridemia and to have correspondingly higher fasting levels of glucose, cholesterol and triglycerides. Insulin resistance was also significantly associated with hepatocellular carcinoma arising in patients with cryptogenic cirrhosis. Current BMI was similar between cases and controls but "precirrhosis BMI" was significantly higher in the cases. Curiously, serum aminotransferases were significantly lower in cases compared with controls. A multivariate analysis showed that hypertriglyceridemia, type 2 diabetes and normal alanine aminotransferase were independently associated with cryptogenic cirrhosis and hepatocellular carcinoma. The importance of these findings remains to be defined, but one could speculate that hepatocellular carcinoma is part of the clinical spectrum of NAFLD and the metabolic derangement observed in patients with NAFLD may underlie the progression of liver disease to cirrhosis and hepatocellular carcinoma.

REPORTS OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH NON-ALCOHOLIC-FATTY LIVER DISEASE

Few reports have been published so far about the incidence of primary hepatic carcinoma in patients with NAFLD and NASH. In 1998, a British group excluded hepatitis G virus as a risk factor for hepatocellular carcinoma, but also noticed that patients with cryptogenic cirrhosis who had developed hepatocellular carcinoma had histological features of NASH.[4]

In 2001, a Japanese group reported a case of NASH with multicentric hepatocellular carcinoma in a female patient.[9] At the age of 58 years, the patient was diagnosed with non-insulin-dependent diabetes mellitus, treated by insulin therapy. She was negative for all serological markers of hepatitis B and C virus infection and denied consuming alcohol. Because of liver dysfunction, a needle biopsy was performed at the age of 62 years and pathological findings, such as fatty change, Mallory's body, nuclear glycogen and pericellular fibrosis, suggested a diagnosis of NASH. Subsequently, four nodules were detected in the liver by imaging, and needle biopsy of the nodules confirmed the diagnosis of hepatocellular carcinoma. Cancer was diagnosed 10 years after the diagnosis of NASH. The authors suggested that hepatocellular carcinoma could be a late complication of NASH.

Shimada et al reported six patients with hepatocellular carcinoma in a group of 82 patients with NASH,[10]

three of whom were referred with hepatocellular carcinoma. In five of these six patients, NASH was associated with obesity, hyperlipidemia or diabetes mellitus. The carcinomas measured 1.5-6.0 cm in size and were well differentiated in three of the six cases. Since fibrosis and cirrhosis were present in all patients with NASH complicated by hepatocellular carcinoma, patients at risk probably could by identified by the same histological and clinical markers that herald disease progression in uncomplicated NASH.

In another single American centre study, one hundred and five consecutive patients with hepatocellular carcinoma were studied.[11] The most common etiology of underlying liver disease was hepatitis C (51%) and cryptogenic cirrhosis (29%). Half of the patients with cryptogenic cirrhosis had histological or clinical features associated with NAFLD, so NAFLD accounted for at least 13% of the cases of hepatocellular carcinoma. Patients with cryptogenic cirrhosis were less likely to have undergone surveillance for hepatoma and had larger tumors at diagnosis. Ultrasound examination in combination with alfa-fetoprotein and des-γ-carboxyprothrombin (a newer marker) every three months appears to be a sensitive and intensive surveillance programme for the early detection of hepatocellular carcinoma.

Finally, in an Italian retrospective study, among 641 patients with cirrhosis associated hepatocellular carcinomas, 44 patients with cryptogenic cirrhosis were identified.[5] Of these, 23 were actively followed up and were compared in a case-control study with viral and alcohol associated hepatocellular carcinoma. Although liver function was similar, cryptogenic cirrhosis patients had higher glucose, cholesterol and triglyceride plasma levels, increased parameters of insuline resistance, and lower aminotransferase levels. Logistic regression analysis identified in sequence hypertriglyceridemia, diabetes and normal aminotransferases as independent factors associated with hepatocellular carcinoma arising in cryptogenic cirrhosis. Thus, features suggestive of NASH were more frequently observed in hepatocellular carcinoma arising in patients with cryptogenic cirrhosis than in age and sex matched hepatocellular carcinoma patients of well-defined viral or alcoholic etiology. The authors conclude that hepatocellular carcinoma may represent a late complication of NASH-related cirrhosis.

CONCLUSIONS

NAFLD appears to be a common cause of the underlying liver disease in patients with hepatocellular carcinoma, but a prospective study of patients with NASH is necessary to confirm the etiologic association and to determine the risk of development of hepatocellular carcinoma in this population. NAFLD may be an important cause of cryptogenic cirrhosis as well as hepatocellular carcinoma.

In conclusion, the whole spectrum of liver disease may stem from a metabolic derangement and attempts should be made to interrupt the progression from simple fatty liver disease to steatohepatitis, fibrosis, cirrhosis and ultimately hepatocellular carcinoma. A behavioural approach, such as diet and exercise, to reduce the prevalence and the progression of obesity, diabetes and dyslipidemia, as well as the pharmacologic treatment of insulin resistance and the use of newer therapeutic agents of NASH, merit consideration in this clinical setting.[12]

REFERENCES

1. Angulo P. Non alcoholic fatty liver disease. N Engl J Med 2002; 346:1221-1231.
2. Ong JP, Younossi ZM. Is hepatocellular carcinoma part of the natural history of nonalcoholic steatohepatitis? Gastroenterology 2002; 123:375-378.
3. Matteoni CA, Younossi ZM, Gramlich T, Bopari N, Liu YC, McCullough AJ. Nonalcoholic faty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999; 116:1413-1419.
4. Hollingsworth RC, Minton EJ, Fraser-Moodie C, et al. Hepatitis G infection: role in cryptogenic chronic liver disease and primary liver cell cancer in the UK. Journal of Viral Hepatitis 1998; 5:165-169.
5. Bugianesi E, Leone N, Vanni E, et al. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. Gastroenterology 2002; 123:134-140.
6. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. Hepatology 1999; 30:1356-1362.
7. Caldwell SH, Oelsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. Hepatology 1999; 29:664-669.
8. Yang S, Lin HZ, Hwang J, Chacko VP, Diehl AM. Hepatic hyperplasia in noncirrhotic fatty livers: is obesity-related hepatic steatosis a premalignant condition? Cancer Res 2001; 61:5016-5023.
9. Zen Y, Katayanagi K, Tsuneyama K, Harada K, Araki I, Nakanuma Y. Hepatocellular carcinoma arising in non-alcoholic steatohepatitis. Pathology International 2001; 51:127-131.
10. Shimada M, Hashimoto E, Hayashi N, Takasdaki K. Hepatocellular carcinoma arising in non-alcoholic steatohepatitis (abstr). Hepatology 2001; 34:459A.
11. Marrero JA, Fontana RJ, Su GL, Conjeevaram HS, Emick DM, Lok AS. NAFLD may be a common underlying liver

disease in patients with hepatocellular carcinoma in the United States. Hepatology 2002; 36:1349-1354.
12. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Zoli M, Mechionda N. Metformin in non-alcoholic steatohepatitis. Lancet 2001; 358:893-894.