Late complications of NASH: a challenge for hepatologists

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Long-term outcomes of cirrhosis in nonalcoholic steatohepatitis compared with hepatitis C. Hui JM, Kench JG, Chitturi S, Sud A, Farrell GC, Byth K, Hall P, Khan M, George J.

Data on the long-term outcome of nonalcoholic steatohepatitis (NASH)-associated cirrhosis are few, and most reports describe cases of cryptogenic cirrhosis associated with risk factors for NASH but without histologic definition. In this prospective cohort study, we describe the long-term morbidity and mortality of 23 patients with NASH-associated cirrhosis defined by strict clinicopathologic criteria. Outcomes were compared with 46 age- and gender-matched patients with cirrhosis from chronic hepatitis C virus (HCV) infection: 23 untreated and 23 nonresponders to antiviral therapy. During follow-up (mean, 84 months; median, 60 months; range, 5–177 months), 9 of the 23 NASH-associated cirrhosis cases developed liver-related morbidity (8 ascites and/or encephalopathy, 1 variceal bleeding). The probability of complication-free survival was 83, 77, and 48% at 1, 3, and 10 years, respectively, and the cumulative probability of overall survival was 95, 90, and 84% at 1, 3, and 10 years, respectively. Five deaths were from liver failure, 1 from a non-liver-related cause. By multivariate analysis, bilirubin ($P=0.02$) and platelet ($P=0.04$) were independent predictors of complication-free survival; bilirubin ($P=0.05$) was the only predictor for overall survival. After controlling for these factors, there was no difference in complication-free or overall survival between the NASH-cirrhosis cohort and either group of HCV-cirrhosis. However, 8 cases of liver cancer occurred in the HCV-cirrhosis groups compared with none among NASH cases. In conclusion, liver failure is the main cause of morbidity and mortality in NASH-associated cirrhosis. The prognosis is either similar or less severe than HCV-cirrhosis, except that HCC appears less common.

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Non-alcoholic fatty liver disease (NAFLD) is becoming the most common liver problem in Western countries as the result of a striking increase in the prevalence of its risk factors, mainly obesity and Type 2 diabetes.

Mounting evidence indicates that a few patients with NAFLD may eventually develop the most worrisome complications of chronic liver disease, i.e. cirrhosis and hepatocellular carcinoma (HCC). The natural history of NAFLD is difficult to assess because most studies were retrospective, lacked systematic follow-up or involved small numbers of highly selected subjects. There is evidence that the progressive form of NAFLD, i.e. nonalcoholic steatohepatitis (NASH) may progress to advanced liver failure, but histologic steatosis tends to diminish or disappear as NASH progresses to cirrhosis. This explains why only 2.6% of patients considered for liver transplantation have been previously diagnosed with NAFLD-related liver disease, whereas up to 70% of patients with cryptogenic cirrhosis show clinical and demographic features suggestive of NASH [1]. In 15–50% of patients with hepatocellular carcinoma (HCC), no etiologic factors of underlying liver disease can be identified [2]. Retrospective, case-control studies have shown that features suggestive of NASH are more frequent in HCC complicating cryptogenic cirrhosis than in matched HCC patients with known etiology [2].

The study performed by Hui and co-workers [3] is the only prospective cohort study so far available on the long-term morbidity and mortality of NASH-associated cirrhosis. The authors defined NASH-associated cirrhosis using strict clinico-pathologic criteria: all patients had an alcohol intake <40 g/week, a >5-year history of clinical risk factors, and steatosis at liver biopsy; in addition, the majority (20/23 patients) had an earlier biopsy specimen demonstrating NASH. Outcomes were compared with matched patients with cirrhosis related to chronic hepatitis C virus (HCV) infection. During a median follow-up of 5 years, 38% of the NASH-associated cirrhosis cases developed liver-related morbidity compared with 55 and 38% of untreated and nonresponders HCV-patients, respectively. Notably, HCC developed in 17% of the HCV-related cirrhosis, but in not one case developed in the NASH group. Although metabolic and vascular disease were more common at entry in NASH, no patient died from vascular complications, liver failure being the cause of death in 5/6 of them. The authors concluded that liver failure is the main cause of morbidity and mortality in NASH-associated cirrhosis, and that the prognosis is either similar or less severe than HCV-cirrhosis, except that HCC is less common.

This interesting study gives us the opportunity to point out some unsettled issues.

Hepatology units attract patients with an overt chronic liver disease, but may miss those with a subclinical course,

arguably a much larger number in the general population. Patients with asymptomatic progression of NASH will silently develop subacute liver failure [1]. Liver disease in NAFLD subjects observed in metabolic/diabetic units is by no means less severe than that observed in hepatology units: at liver biopsy, unexpected cirrhosis can be found in 10% of overweight patients [4] and in diabetes the mortality rate for cirrhosis is increased by 2.5 fold [5].

When comparing the natural history of NASH-related cirrhosis, the choice of appropriate paired controls is critical and difficult. In Hui's study, 38% of the patients with HCV-related cirrhosis showed histologic features of metabolic liver disease, such as ballooning degeneration. An association of HCV infection with steatosis and features of the metabolic syndrome and has been repeatedly reported [6]. While the diagnosis of NASH is made by exclusion of all the known causes of liver disease, the same is not usually done for cirrhosis of known etiology. Thus, a concomitant occult NASH may contribute to the onset of complications in viral, autoimmune or toxic cirrhosis.

A major drawback of prospective NASH studies is that they are too short at present to definitely exclude late complications. A surprising finding in this study is the absence of HCC as a complication of NASH-associated cirrhosis after a mean follow-up of 7 years (median 5 years). As the authors acknowledge, in a retrospective series of 23 cases with cryptogenic cirrhosis complicated by HCC the average length of cirrhosis before the diagnosis of HCC was 14 ± 6 years [7]. Thus, a longer follow-up and larger cohorts may be required to determine the actual incidence of HCC in NASH-associated cirrhosis.

Of note, obesity and diabetes per se are significantly associated with the development of HCC. Mortality rate from liver cancer was recently found to be 5 times higher in subjects with BMI >35 [8] and diabetes increased the risk of HCC by 1.3–2.4 fold [2]. In consideration of the growing epidemics of metabolic diseases in western countries, a small increase in HCC risk due to obesity and diabetes could translate into a large number of HCC cases in the general population.

Although hepatocellular failure was the leading cause of death in patients with NASH-associated cirrhosis, none of them underwent orthotopic liver transplantation (OLT) compared with 3/46 of the HCV patients. End-stage liver disease secondary to cryptogenic cirrhosis is the indication for liver transplant in 7–14% of the recipients. However, in NASH limits to this therapeutic opportunity are posed by older age, the concurrent presence of severe metabolic or vascular disease and finally a possible delay in diagnosis and lack of systematic surveillance.

The prevalence of metabolic complications in NAFLD is unexpectedly low, in spite of diabetes. In cirrhosis, the presence of diabetes poses an increased risk of hepatocellular failure, not of diabetes-related complications [9]. By reducing arterial pressure, hyperlipidemia, platelets and clotting factors, chronic liver disease might protect from cardiovascular risk [10], but there is also the possibility that NASH patients with severe metabolic and cardiovascular complications are no longer referred to hepatologists.

NASH share with HCV-associated chronic infection a silent onset, an asymptomatic course and a 20–30 year time lag before liver disease becomes overt. It will take a few years more before we can reach a good definition of the natural history of disease. This is mandatory for treatment options: should all patients be treated, or should treatment be limited to those who progress to end-stage liver disease? When should treatment be initiated? Thus, despite a lot of difficulties, long-term prospective studies of natural history remain a high priority in the research agenda of NASH, and studies like those by Hui and co-workers are eagerly awaited.

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