Session I

EPIDEMIOLOGY, DIAGNOSIS AND DEFINITION OF NASH

EPIDEMIOLOGY OF FATTY LIVER IN NASH AND ASH

Stefano Bellentani andClaudio Tiribelli, Fondo Studio Malattie del Fegato and Azienda U.S.L. de Modena, Italy, email: liversb@unimo.it.

Though the finding of fatty liver (FL) is becoming increasingly frequent in clinical practice, its prevalence, especially in the general population is largely unknown. The prevalence of NASH in a series of patients who underwent to liver biopsy was 7 – 9% in Western patients and 1 – 2% in Japanese patients. The prevalence of FL differs according to the age, alcohol and drug consumption, presence of other diseases, diabetes, obesity and hyperlipoproteinemia in particular. To study the true prevalence of FL, we took advantage of the ongoing Dionysos study (a cohort study on the epidemiology of chronic liver disease performed in the general population of 2 towns in Northern Italy), and performed a cross-sectional, observational study among the 6917 participants. Ethanol intake, assessed by a validated questionnaire and expressed as daily (g/day) and life (kg) consumption, and body mass index were assessed in 257 subjects, divided in 4 categories (67 control, 66 obese, 69 heavy drinker, and 55 obese and heavy drinker). Biochemical tests exploring both liver and metabolic functions and hepatic ultrasonography were performed also. The prevalence of FL increased from control (16%) to heavy drinkers (46%, obese (76%), and obese and heavy drinkers (94.5%). Elevation of alanino-aminotransferase (ALT) and triglycerides (TG) were the more reliable markers of FL. According to persistent alteration of ALT, GGT and TG, but not confirmed by liver biopsy (for ethical reason), NASH could be suspected in 30% of obese with FL and ASH in 40% of heavy drinkers with FL. Persistent alteration of blood tests suggesting hepatitis were present in 70% of obese and heavy drinkers. On these grounds we conclude that FL is frequently encountered in healthy subjects (16%) and that the prevalence of both FL and NASH or ASH are different according to the presence of obesity, heavy drinking or both. FL and persistent alteration of blood tests of inflammation are almost always present in obese subjects drinking more than 60 g/alcohol per day.

THE PATHOLOGY AND CLASSIFICATION OF NASH

Jurgen Ludwig, Rochester

Pathology

By definition, the histologic features of nonalcoholic steatohepatitis (NASH) are indistinguishable from those of alcoholic liver disease. Three main histologic manifestation exist:

***Macrovesicular** fatty change without fibrosis and with only minimal inflammation. Biopsy samples of this type overlap with uncomplicated fatty (non-inflammatory) change and may reflect a nonprogressive course. Connective tissue stains should be prepared, even minimal centrilobular fibrosis may indicate progressive disease.

***Macrovesicular** fatty change with moderate, primarily centrilobular mixed inflammatory infiltrates, with or without prominent hepatocellular damage and Mallory bodies, and perivenular and perisinusoial fibrosis in zone 3 of the acini. These manifestations represent slowly progressive disease and may lead to steatohepatitic cirrhosis.

***Submassive** hepatic necrosis with fatty change, central-to-central bridging necrosis, mixed inflammatory infiltrates and Mallory bodies. This pattern represents a very rare manifestation of progressive NASH which may lead to hepatic failure and death within a few months after onset of the disease.

Classification

Inactive NASH or Nonalcoholic Fatty Liver. Probably the most common manifestations of the condition. The disease appears to be nonprogressive in many instances but continued observation is indicated.

Chronic NASH. Most cases appear to be slowly progressive; patients should be considered for treatment trials.

Subacute (subfulminant) NASH. This rare variant of NASH may occur after precipitating events, typically associated with rapid weight loss, such as excessive fasting in morbid obesity or weight-reducing surgery. The condition often is fatal; biopsy material is rarely obtained.

Differential Diagnosis

Chronic hepatitis C or steroid-treated autoimmune hepatitis, early-stage Wilson's disease, and focal fatty change are among the conditions that may be mistaken for NASH. In the absence or centrilobular inflammation and fibrosis conditions other than NASH or ASH should be considered. An appropriate clinical history, tests for hepatitis C and autoantibodies, and in you patients, tissue copper analysis should be included in the diagnostic armamentarium. The diagnosis of focal fatty change may require ultrasound studies or other imaging procedures. Thus, fatty changes and inflammation alone do not constitute NASH. In the presence of cirrhosis, conditions such as chronic hepatitis C and autoimmune hepatitis still may be mistaken for NASH. On the other hand, NASH may not be considered if fat has disappeared. Therefore, NASH should be included among the possible causes of cryptogenic cirrhosis.

HISTOLOGICAL GRADING AND STAGING FOR NONALCOHOLIC STEATOHEPATITIS

Elizabeth M. Brunt, MD, Department of Pathology, Saint Louis University Health Sciences Center, St. Louis, MO 63110 USA

Unlike other forms of chronic liver disease for which serologic assays are useful in diagnosis, the diagnosis of nonalcoholic steatohepatitis (NASH) is one of clinical-pathologic correlation. Liver biopsy serves two purposes in NASH: to establish the diagnosis, and to assess progressive liver injury. Systematic reporting of the various histologic lesions in other chronic liver diseases is accepted in current medical practice for clinical evaluation and for assessing efficacy of therapeutic interventions. A reproducible and standard evaluation of NASH could also serve these purposes. Systems published for recroinflammatory activity (grade) and collagen deposition (stage) for other forms of chronic liver disease are not readily transposed to the lesions of NASH, however, because the unique necroinflammatory and fibrotic lesions of NASH, noted primarily in the lobules, are not similar to the predominantly portal-based inflammation and fibrosis of chronic viral hepatitic, metabolic and cholestatic liver diseases.

The proposed system was based on a review of 51 biopsies from NASH patients. Following a global impression recorded for grade and stage, several histologic variables were separately scored: steatosis (type, zone, and percent of lobule involved), hepatocyte injury (ballooning, Mallory's hyaline, acidophil bodies, PASd Kupffer cells), intralobular inflammation (location, cell types and quantity), portal inflammation, glycogenated nuclei, and collagen deposition (zonal localization, extent). The working formulae for grade and stage were derived by analyzing factors associated with progressive injury. For grade (Table 1) the combinations of variables of significance were noted to be steatosis, ballooning, and lobular and portal inflammation. Stage (Table 2) was determined by the deposition of collagen, initially in zone 3 pericellular or perisinusoidal spaces, with subsequent portal and bridging fibrosis, and ultimately cirrhotic remodeling.

TABLE 1: GLOBAL GRADE FOR NASH

GRADE	STEATOSIS*	BALLOONING	INFLAMMATION**
Mild, grade 1	1-2	Minimal	L: 1-2 P: None-Mild
Moderate, grade 2	2-3	Present-zone 3	L: 2 P: Mild-Moderate
Severe, grade 3	3	Marked-zone 3	L: 3 P: Mild-Moderate

*1=≤33%, 2=>33%≤66%, 3=>66% **L = Lobular, (foci/20x), P = Portal

TABLE 2: FIBROSIS SCORE FOR NASH

Stage	Zone 3 Fibrosis	Portal Fibrosis	Bridging Fibrosis	Cirrhosis
1	**Pericellular, perisinusoidal, Focal or extensive**	**0**	**0**	**0**
2	**As above**	**Portal, periportal fibrosis, Focal or extensive**	**0**	**0**
3	**Bridging septa**	**Bridging septa**	**+**	**0**
4	**+/-; zone 3 may be incorporated into septa**	**Portal tracts may be replaced or incorporated into septa**	**Extensive**	**+**

DIAGNOSIS OF NON-ALCOHOLIC FATTY LIVER

OFW James – Newcastle upon Tyne, UK

While the presence and even, to some extent, the severity of fatty infiltration of the liver can now be made reliable by ultrasound three important considerations remain in making a diagnosis and giving a prognosis for each individual patient.

1. To confirm that non-alcoholic fatty live (NAFL) is the true diagnosis.
2. To examine possible causes or association.
3. To decide whether liver biopsy is necessary.

(1) To confirm the diagnosis of NAFL other liver diseases must be excluded. In respect of alcoholic liver disease (ALD) liver function tests are not very helpful since transaminases and gamma glutamyl transpeptidase are raised in both. An ALT/AST ratio of >1 is more suggestive of NAFL, although in severe NAFL AST is often more elevated than ALT – as in ALD. Raised MCV is also more suggestive of ALD. Strict and very thorough exclusion of possible alcoholic aetiology should also be made through repeated questioning and corroboration, where possible, by significant others and the primary care physician. Other possible causes of liver disease with fat – particularly hepatitis C – should be excluded by appropriate serology.

(2) In consideration of possible causes/associations for NAFL the following should be evaluated. Full medication history, past medical/surgical history (?weight reduction

surgery), possible glucose intolerance – Type II diabetes, lipid profile, body mass index, waist-hip ratio (for central obesity).

(3) While it is impossible at present to reliably assess degree of inflammation or fibrosis in the presence of steatosis without liver biopsy we now know enough to make some pragmatic observations. Three large studies have all shown that in adults under age 40 significant liver inflammation or fibrosis are extremely rare in NAFL except in patients with previous weight reducing surgery. Except in the situation of a clinical trial it now seems unnecessary to do liver biopsy on such individuals. Risk of fibrosis/cirrhosis and necro inflammation increases with age above 40; other main risks appear to be Type II diabetes and greater degrees of obesity. For diagnosis, and particularly for prognosis, I recommend liver biopsy in patients over age 40 in whom NAFL is strongly suspected by virtue of:

i. Persistently abnormal LFT (transaminases, gamma GT)
ii. Fatty liver on ultrasound.
iii. Exclusion of other causes by appropriate history and serology

CLINICAL COURSE AND PROGNOSIS OF NON-ALCOHOLIC STEATOHEPATITIS (NASH)

Bruce R. Bacon, MD, Division of Gastroenterology and Hepatology, Saint Louis University School of Medicine, St. Louis, Missouri, USA

Most patients with nonalcoholic steatohepatitis (NASH) are identified because of an evaluation either of elevated liver enzymes or of hepatomegaly determined on routine physical examination. They usually do not have symptoms. When patients do have symptoms, they may complain of dull right upper quadrant pain, which is probably caused by distention of Glisson's capsule. They also may have a variety of less common nonspecific symptoms such weakness, fatigue, and malaise. The prevalence of these symptoms in patients with alcoholic steatohepatitis (ASH) is much greater. Palpable hepatomegaly is the most common physical finding that is identified in patients with NASH. In patients who progress to develop cirrhosis, the usual physical examination findings of cirrhosis are identified. Serum aminotransferases are usually elevated at the time of diagnosis but can also be normal in patients who have histologis findings of NASH. Most series of NASH patients have elevated liver enzymes because that is the way that patients came to me medical attention. The ALT level is typically higher than the AST level in NASH, unless liver disease has progressed to cirrhosis. Gamma-glutamyltranspeptidase levels are frequently elevated in patients with NASH. Lipid abnormalities and disorders of glucose homeostatis are commonly seen in patients with NASH.

Liver biopsy shows a significant increase in fibrosis in about 40% of patients and cirrhosis in about 15% of patients. Thus, NASH can be a progressive and serious disease. However, the rate of progression is poorly understood. In patients who are obese, who have uncontrolled diabetes or elevated lipids, it is reasonable to suggest weight loss, control of diabetes, and dietary maneuvers to reduce elevated lipids. Weight loss is generally associated with normalization of serum aminotransferases and in reduction in fat identified by imaging, but it is not clear that these changes affect long-term prognosis. A summary of studies in which serial liver biopsies were performed shows that about 50% of patients progress (increase in fibrosis) over a 4 to 5 year time period and the rest remain stable. Thus, prognosis is worrisome in those patients who have an increase in fibrosis as they very well may progress to cirrhosis. Generally, however, the rate of fibrotic progression in NASH appears to be less rapid than that for hepatitis C.

Taken from Abstracts, Poster Abstracts….Steatohepatitis (NASH and ASH)
Falk Symposium NO. 121 – October 14-15, 2000
Den Haag (Netherlands)

Tomorrow is Section II – Pathogenic Mechanisms of NASH and ASH (Part I)