Non-Alcoholic Fatty Liver Disease:

A Benign Bystander or an Epidemic?

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Non-alcoholic fatty liver disease (NAFLD) describes a spectrum of clinical-pathologic conditions ranging from benign steatosis to non-alcoholic steatohepatitis (NASH). It is becoming increasingly common with an estimated prevalence in the general population of approximately 20%.[1] The spectrum of clinical disease seen in NAFLD can range from a persistently asymptomatic state to decompensated cirrhosis.

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Difference between benign steatosis and NASH

The unifying feature of all conditions under the umbrella term NAFLD is steatosis affecting > 5% of hepatocytes on liver biopsy. The histologic presence NASH or absence (benign steatosis) of significant necroinflammatory injury further defines this group of conditions. Thus, although features of history, laboratory tests and imaging may be strongly suggestive of NAFLD, it remains histologically defined. Hepatic steatosis on its own is thought to represent a benign process less likely to progress to overt clinical disease, whereas NASH may, over time, progress to cirrhosis with its associated complications.

Magnitude of the problem

The prevalence of NAFLD and NASH in the general adult population is approximately 20%[1] and 3%, respectively.[2] In comparison, current data suggests approximately 50% of diabetics and up to 74% of obese persons have NAFLD.[3] Up to 50% of morbidly obese patients have NASH.[3] In addition, the full spectrum of NAFLD is also seen in children and it is estimated that approximately 3% of children four- to 12-years-of-age have NAFLD.[4]

Natural history

The natural history of NAFLD remains incompletely defined and the seemingly intuitive progression from steatosis to NASH to eventual cirrhosis may not be an accurate depiction of the disease process. Approximately 15% of those with steatosis will have NASH.[2] Of those with NASH, approximately one-third will develop progressive fibrosis, with a third of those individuals progressing to cirrhosis.[5]

Risk factors for NAFLD

- Obesity
- Diabetes
- Hyperlipidemia (in particular, hypertriglyceridemia)
- Medications (corticosteroids, estrogens, calcium channel blockers, methotrexate)
- Rapid weight loss
- Family history of NASH or cryptogenic cirrhosis

Clinical features

The majority of patients with NAFLD will be asymptomatic. However, fatigue, malaise and right upper quadrant fullness or tenderness may be present. On physical examination, elevated BMI, hepatomegaly and signs of chronic liver disease (if advanced disease with cirrhosis is present) may be found. A history of significant alcohol consumption (> 20 g/day) should be absent.

Laboratory findings

Elevated hepatocellular liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) are the most common (and often the only) laboratory abnormality found in NAFLD. The magnitude of the elevation is usually two to four times the upper limit of normal (ULN) and elevations > 10 times the ULN would be unusual. The ratio of AST/ALT may be helpful and is usually less than one (in contrast to alcohol-induced liver disease, in which the ratio is usually greater than one). However, as NASH progresses, this ratio may eventually reverse in the presence of advancing fibrosis. Although one would expect normal liver biochemical tests in benign steatosis, normal biochemistry does not rule out NASH or advanced fibrosis/cirrhosis.

Mildly elevated cholestatic liver enzymes (alkaline phosphatase, gamma-glutamyltransferase), either alone or in combination with elevated hepatocellular liver enzymes, may also be seen.

Imaging

Ultrasound is a useful, easily accessible diagnostic test, with an ability to detect steatosis with a sensitivity and specificity of 89% and 93%, respectively.[6] In addition, imaging is helpful to screen for the presence of advanced fibrosis/cirrhosis.

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Management

A number of studies have investigated the role of medical therapy in the treatment of NAFLD. In particular, there is some promising evidence that insulin sensitizers such as pioglitazone[7] and metformin[8,9] may be beneficial in improving both biochemical and histologic abnormalities in NAFLD. However, the results are preliminary and larger, longer-term trials are needed.

FAQ

When should I refer to a liver specialist?

If liver enzymes remain persistently elevated for > 6 months, the diagnosis is in question, or clinical suspicion of advanced liver disease is present, referral in order to rule out other potential causes of liver disease and consideration for liver biopsy and other therapies is warranted.

Due to the lack of a definitive medical therapy for NAFLD, management is focused on identifying and treating risk factors (diabetes, hyperlipidemia) and on lifestyle modification (diet, aerobic exercise). Target weight loss of approximately 10% of total body weight should be gradual, as more rapid weight loss (> 1.6 kg/week) may worsen the condition.[10]

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Take-home message

1. Many patients with non-alcoholic fatty liver disease have benign steatosis, but some have non-alcoholic steatohepatitis which can progress to cirrhosis
2. Liver biopsy is the only way to definitively establish the diagnosis
3. Risk factor modification, weight loss and dietary changes represent the mainstays of therapy

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