FATTY LIVER

Introduction

Non-alcoholic fatty liver disease (NAFLD) refers to the presence of **hepatic steatosis** when no other causes for secondary hepatic fat accumulation (e.g., heavy alcohol consumption) are present.

NAFLD is important to recognize, as it may progress to cirrhosis and is likely an important cause of cryptogenic cirrhosis.

Definitions:

Patients with non-alcoholic fatty liver disease (**NAFLD**) have:

- Hepatic steatosis,

With or without:

- Inflammation and fibrosis.

In addition, **no secondary causes** of hepatic steatosis are present.

NAFLD is subdivided into:

1. Non-alcoholic fatty liver (**NAFL**)
    - In NAFL, hepatic steatosis is present *without* evidence of significant inflammation.
2. Non-alcoholic steatohepatitis (**NASH**).
    - In NASH, hepatic steatosis is associated with *hepatic inflammation*.

      This may be histologically indistinguishable from alcoholic steatohepatitis.

Patients with fatty liver, should be referred to **Gastroenterology** for formal diagnosis and development of a surveillance plan.

Epidemiology

Non-alcoholic fatty liver disease is seen worldwide and is the most common liver disorder in Western industrialized countries, where the major risk factors for NAFLD, (see below) are common.

Most patients diagnosed with NAFLD are in in their 40s or 50s

Pathology

The exact pathogenesis of **non-alcoholic fatty liver disease** has not been determined.

The most widely held theory implicates **insulin resistance** as the key mechanism leading to hepatic steatosis, and perhaps also to steatohepatitis.

Others have proposed that an additional insult in the form of an "oxidative" injury, is required to manifest the necro-inflammatory component of steatohepatitis. Hepatic iron, leptin, antioxidant deficiencies, and intestinal bacteria have all been suggested as potential oxidative stressors.

Risk factors:

The major risk factors for Non-alcoholic fatty liver disease include:

1. Central obesity
2. Type 2 diabetes mellitus / metabolic syndrome (i.e. insulin resistance syndrome)
3. Dyslipidaemia
4. Systemic hypertension

Less certain correlations are with:

1. Previous cholecystectomy (less certain)
2. Polycystic ovary syndrome
3. Hypothyroidism
4. Obstructive sleep apnea
5. Hypopituitarism
6. Hypogonadism

Natural History:

Patients with non-alcoholic fatty liver disease may eventually develop **cirrhosis** (roughly one third).

Cirrhosis develops when simple steatosis progresses to steatohepatitis and then fibrosis.

Among patients with **cryptogenic cirrhosis**, up to 70 % have risk factors for NAFLD.

Patients with simple steatosis on biopsy are at low risk for developing significant fibrosis, whereas those with non-alcoholic steatohepatitis are at higher risk.

Some patients with fibrosis, however, may show regression of their disease.

Differential diagnoses:

Note that there are also *other* causes of **hepatic steatosis** (i.e. apart from NAFLD)

Causes of hepatic steatosis in addition to NAFLD include:

1. Alcoholic liver disease
2. Hepatitis C (particularly genotype 3)
3. Wilson's disease
4. Starvation
5. Medications:

   Implicated agents include:

   - Amiodarone, methotrexate, tamoxifen, glucocorticoids, valproate, anti-retroviral agents for HIV.

5. Reye syndrome:
6. Acute fatty liver of pregnancy
7. Inborn errors of metabolism (LCAT deficiency, cholesterol ester storage disease, Wolman disease)

Clinical features

Most patients with non-alcoholic fatty liver disease (NAFLD) are **asymptomatic**.

Some patients with non-alcoholic steatohepatitis (**NASH**) may have symptoms including:

1. Fatigue/ lethargy / malaise

2. Vague right upper abdominal discomfort

In general however, patients usually come to attention because of:

1. Laboratory testing revealing elevated liver aminotransferases

2. Hepatic steatosis detected incidentally on abdominal imaging.

3. Clinical hepatomegaly:

    - Patients with NAFLD may have hepatomegaly on physical examination due to **fatty infiltration** of the liver.

Patients who present late and have developed **cirrhosis** may have the classical stigmata of chronic liver disease (e.g., palmar erythema, spider angiomata, ascites).

Making the Diagnosis:

The formal diagnosis of non-alcoholic fatty liver disease (NAFLD) requires *all* of the following:

1. Demonstration of hepatic steatosis by imaging or biopsy

2. Exclusion of significant alcohol consumption

3. Exclusion of other causes of hepatic steatosis

4. Absence of coexisting chronic liver disease

Investigations

Blood tests

1. FBE:

    The following may be associated in patients with cirrhosis:

    - Thrombocytopenia

    - Neutropenia

2. U&S/ glucose

3. LFTs:

    - ALT/AST:

Patients with NAFLD frequently have mild to moderate elevations in the aspartate aminotransferase (AST) and alanine aminotransferase (ALT), although normal aminotransferase levels *do not* exclude early NAFLD.

When elevated, the AST and ALT are typically 2 -5 times the upper limit of normal, with an AST to ALT ratio of <1, (in distinction to **alcoholic** fatty liver disease, which typically has a ratio > 2)

it should be noted that the *degree* of aminotransferase elevation does **not** predict the degree of hepatic inflammation or fibrosis, and a *normal* alanine aminotransferase does **not** exclude clinically important histologic injury.

- ALP:

  The alkaline phosphatase (ALP) may be elevated to 2 - 3 times the upper limit of normal.

- Albumin:

  Serum albumin and bilirubin levels are *typically* **within the normal range**, but may be abnormal in patients who have developed **cirrhosis.**

4. Coagulation profile:

   - In patients with cirrhosis, the prothrombin time may be elevated.

5. Iron studies:

   - Patients with NAFLD may have an elevated serum **ferritin** concentration or **transferrin saturation**.

     There is evidence that a serum ferritin > 1.5 times the upper limit of normal in patients with NAFLD is associated with a higher non-alcoholic fatty liver disease activity score (and thus, NASH) and with advanced hepatic fibrosis.

6. Hepatitis virus screening:

   - Patients should also be screened for viral hepatitis A, B and C.

     This is to both to rule out these infections in patients with elevated aminotransferases and to determine the patient's immune status to guide future immunizations.

Ultrasound

Ultrasound findings in patients with NAFLD include:

1. Hepatomegaly

2. Increased echogenicity, (i.e. a hyperechoic liver).

Vibration controlled transient elastography, which is routinely used to grade **fibrosis** based on liver stiffness, is also being developed to grade hepatic steatosis

CT Scan

CT findings in patients with NAFLD include:

1. Hepatomegaly

2. Decreased hepatic attenuation

MRI Scan

MRI findings in patients with NAFLD include:

1. Hepatomegaly

2. Increased fat signal

Note that both CT and MRI can identify **steatosis** but are not sufficiently sensitive to detect *inflammation* or *fibrosis*.

Liver Biopsy

Liver biopsy remains the "gold standard" for the diagnosis of NAFL.

Liver biopsy however *not* indicated for the majority of patients.

It may be indicated:

1. If the diagnosis is not clear.

2. To assess the *degree* of hepatic injury.

3. For differentiation of non-alcoholic fatty liver (NAFL) from non-alcoholic steatohepatitis (NASH).

The NAFLD activity score (NAS) is a validated score that is used to grade **disease activity** in patients with NAFLD.

The NAS is the sum of the biopsy's individual scores for:

- Steatosis (0 to 3)
- Lobular inflammation (0 to 3)
- Hepatocellular ballooning (0 to 2).

Fibrosis is not included in the NAS.

In the study that derived the NAS, scores of:

1. 0 - 2 occurred in cases largely considered not diagnostic of NASH
2. 3 - 4 were evenly divided among those considered not diagnostic, borderline, or positive for NASH
3. 5 - 8 occurred in cases that were largely considered diagnostic of NASH

Management

Multiple therapies have been investigated for the treatment of non-alcoholic fatty liver disease (NAFLD), but there is no proven curative therapy as yet.

The following measures are recommended as helpful:

1. Weight loss:
    - Weight loss is currently the only therapy with reasonable evidence suggesting it is beneficial and safe.

      A reasonable goal for many patients is to lose 0.5 - 1 kg/week
2. Immunization:
    - Hepatitis A and B vaccinations should be given to patients without serologic evidence of immunity.
    - Pneumococcal vaccine should be given.
3. Treatment of any associated risk factors for cardiovascular disease:
    - Patients with NAFLD are at increased risk for cardiovascular disease and often have multiple cardiovascular disease risk factors.

      Management of patients with NAFLD includes optimization of blood glucose control in patients with **diabetes** and treatment of

hyperlipidemia. Statin therapy has been shown to be safe in patients with NAFLD

4. Alcohol avoidance:

   - **Heavy** alcohol use is associated with disease progression among patients with NAFLD.

     Whether light to moderate alcohol consumption is harmful is unknown.

The management of **cirrhosis** due to NAFLD is similar to that for cirrhosis due to other causes and so includes management of portal hypertension, screening for hepatocellular carcinoma, and consideration of liver transplantation for patients with decompensated cirrhosis.

Disposition:

Patients with fatty liver, should be referred to **Gastroenterology** for formal diagnosis and development of a surveillance plan.

References

1. Sunil G Sheth & Sanjiv Chopra et al. Fatty Liver in Up to Date Website, June 2018.

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August 2018.