Steatosis to Steatohepatitis to Cirrhosis

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Hepatic Steatosis

- "Fatty Liver"
- "Fatty Infiltration of the Liver"
- Becoming increasingly common

Causes of Hepatic Steatosis

- Obesity
- Diabetes mellitus
- Metabolic Syndrome
- Alcohol (3 drinks/day for men, 2 drinks/day for women)
- Hepatitis C (Especially Genotype 3)
- Wilsons Disease
- TPN

Drug-induced steatosis

- Amiodarone
- Valproic acid
- Tamoxifen
- Methotrexate
- Tetracycline

Pathogenesis

- Not totally clear, but insulin resistance key
- “Second Hit” or additional oxidative injury needed to cause the necroinflammatory component of steatohepatitis

Steatohepatitis

- Steatosis plus inflammation
- Two main types: alcohol and nonalcohol-related-
- (NASH)
- Steatohepatitis may progress to cirrhosis
- NASH a frequent cause of unexplained (cryptogenic) cirrhosis

Prevalence of NAFLD

- Nonalcoholic Fatty Liver Disease (NAFLD) has increased worldwide over the past 30 years
- 12-25% in U.S. w/NAFLD, 2-12% w/NASH
- NASH leading cause of cryptogenic cirrhosis
- 30% of patients with NAFLD may have NASH (nonalcoholic steatohepatitis)-inflammation
- NASH may progress to cirrhosis in 20% of cases

Progression to Fibrosis

- Rate of progression is slow: 7.5 years to progress one stage
- Progression to cirrhosis and decompensation 3% over 7.5 years
- Men and postmenopausal women are at greatest risk of fibrosis

Insulin Resistance And NAFLD

- Insulin resistance leads to more fat in liver:
- 1. Increased lipolysis
- 2. Increased triglyceride synthesis
- 3. Increased hepatic uptake of free fatty acids
- 4. Increased accumulation/ hepatic triglycerides

Regulators of Hepatic Insulin Sensitivity

- Fat-derived hormones (produced in adipose)
- 1. Adiponectin-regulates glucose/FA levels
- 2. Leptin-regulates fat storage and appetite
- 3. Resistin-link between obesity and Type 2 DM

Causes of Hepatic Necroinflammation

- Mitochondrial defects
- Impaired free oxygen radical scavenging
- Increased hepatic iron
- Hepatotoxic byproducts of intestinal bacteria

Blood Tests

- Degree of aminotransferase elevation does not predict degree of hepatic inflammation/ fibrosis
- Alkaline phosphatase may be 2-3 times normal
- Serum ferritin/transferrin sat may be elevated
- Ferritin >1.5 times normal a/w NASH & fibrosis

Fibrosure

- Biomarker test that uses results of 6 blood tests to generate a score correlated w/degree of liver damage
- Same prognostic value as liver biopsy
- ALT, alpha 2 macroglobulin, bilirubin, GGT, haptoglobin, apolipoprotein A-1

Diagnosis of NAFLD

- Demonstration of hepatic steatosis by imaging or liver biopsy
- Exclusion of significant alcohol consumption
- Exclusion of other causes of hepatic steatosis
- Absence of coexisting chronic liver disease

Diseases to R/O

- Hepatitis C : anti-HCV antibody
- Hepatitis B: Surface antigen, Surface antibody, Core antibody
- Hemochromatosis: Serum iron, TIBC, ferritin
- Autoimmune hepatitis /cholangitis: ANA, ASMA, anti-LKM antibody, AMA

More Rare Diseases

- Alpha 1-antitrypsin deficiency: alpha 1-antitypsin level
- Wilsons Disease: Ceruloplasmin level

Diagnosis of NASH

- MRI most sensitive for steatosis (>5-6% abnl)
- Liver biopsy is the gold standard to distinguish NASH from NAFLD
- Ultrasound and MRI elastography both test liver fibrosis-fibrotic liver is stiffer

Role of Liver Biopsy

- Exclude concomitant liver disease
- Confirm the diagnosis of NASH
- Stage fibrosis

Grading Inflammation

- Metavir A1: minimal to mild activity
- Metavir A2: moderate activity
- Metavir A3: marked activity /bridging necrosis

Staging Fibrosis

- Metavir F0: no fibrosis
- Metavir F1: mild fibrosis (portal expansion)
- Metavir F2: moderate fibrosis (few bridges)
- Metavir F3: severe fibrosis (numerous bridges)
- Metavir F4: cirrhosis

Treatment of NASH

- No pharmacological treatment approved
- Diet and exercise for weight loss may alter course of the disease
- Antiglycemic drugs may alter disease course by decreasing insulin resistance

Lifestyle Changes and NAFLD Remission

- Weight loss of 7-10% can bring about remission in NAFLD in obese and non obese patients
- Aerobic exercise and resistance training also beneficial
- LIiver enzyme levels, liver fat, and liver histology may all improve

? Drug Therapy

- pioglitazone-decreases insulin resistance
- vitamin E-antioxidant, but RDA only 20 IU/day
- obeticholic acid-in Phase 3 trials for NASH
- liraglutide-increases insulin release/ decreases glucagon release
- elafibranor-improves insulin sensitivity

NAFLD Clinical Presentation

- Elevated aminotransferases (1/3 have elevated alkaline phosphatase)
- >50% have elevated ferritin
- Weakly (+) autoimmune markers
- Abnormal imaging (U/S, CT, MRI)
- 50-60% with hepatomegaly

NAFLD Progression

- 70-75% w/isolated steatosis or steatosis with mild inflammation
- 25-30% with NASH
- NASH may progress to fibrosis> cirrhosis> liver failure or hepatocellular cancer

NASH and OLT

- In 2015 NASH surpassed HCV as the number one indicator for liver transplantation in patients aged less than 50 years of age

NASH and HCC in OLT Candidates

- Hepatitis B and C have been main causes of hepatocellular cancer (HCC)
- Cirrhosis from any etiology may lead to HCC
- NASH is most rapidly growing cause of HCC-fueled by epidemic of obesity and Type 2 DM

Screening for HCC

- Cirrhotic patients, whatever the etiology, should be screened every 6 months for HCC
- Imaging, with ultrasound, CT, or MRI, is standard
- AFP levels are optional