Non-alcoholic Fatty Liver Disease (NAFLD)

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Case

- 12 yo hispanic male presents to clinic after incidental finding of increased liver enzymes
- **PMH:** negative. No h/o transfusions; no drugs/alcohol. No medications/allergies.
- **Fam Hx:** No liver disease. Parents overweight.
- **PE:** weight 66 kg, (>97%), BMI 29. BP 135/80 Acanthosis nigricans. Central obesity: liver and spleen not palpable.
- Pre-op labs before knee surgery:
  - AST 120, ALT 96
Non-alcoholic Fatty Liver Disease (NAFLD)
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*Spectrum* of fatty liver disease that resembles alcohol-induced liver injury, but with little or no alcohol intake.

NAFLD

- Steatosis
- Steatosis + Nonspecific Inflammation
- Steatosis + Hepatocyte Injury + Inflammation

NASH

- Cirrhosis
Pathophysiology

- Multifactorial. Several factors promote intrahepatic accumulation of FFA and changes in insulin mechanisms
  - “Genes propose, environments dispose”
- **GENES:** Multiple gene polymorphisms increase susceptibility
  - Lipid metabolism, inflammation, oxidative stress
- **Environment:**
  - High caloric intake due to poor diet, daily consumption of junk food and high fructose corn syrup, and low levels of physical activity
NAFLD: Prevalence in Pediatrics

- **Autopsy study in peds (accidental death): 9.6% NAFLD**
  - 38% of obese patients had steatosis
  - 23% of all NAFLD had NASH
  - 9% had bridging fibrosis (advanced disease)
  - **Obesity, older age, male gender, and hispanic race were independent predictors of fatty liver**

- **Increasing prevalence**
  - Prevalence has doubled in 20 years. Now in 11% of adolescents
  - 48% of obese males have NAFLD
  - Correlates with increasing # of obese children
    - Obesity (5% → 20%) and severe obesity (1.5% → 5.5%)

- **Youngest patient with NAFLD:** 2yo!!
- **Youngest patient with NASH cirrhosis:** 8yo!!
- **Expected to become the most common cause of pediatric chronic liver disease in the next 10 years**

*J Peds 2013;162, Hepatology 2005; 42*
Who gets NAFLD?

**Increased risk**
- Race (Hispanic)
- Family history
- **Obesity: central**
- DM, insulin resistance
- Metabolic syndrome
  - Insulin resistance
  - HTN
  - Dyslipidemia
- Nutrition: high fructose
- Minimal activity

**Decreased risk**
- Race (African American)
- Normal BMI
- Exercise
  - even if overweight
- Breastfeeding in infancy
  - When breastfed >6mo, children were ½ as likely to develop NAFLD. 17 yr follow-up study
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- **PE:** weight 66 kg, (>97%), BMI 29. BP 135/80
  - **Acanthosis nigricans.** **Central obesity:** liver and spleen not palpable.

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Significance of NASH

- NASH exacerbates liver damage induced by other diseases
  - Alcohol ("ASH"), viral and autoimmune hepatitis
- Decreases pool of donor organs
  - >30% steatosis is an independent predictor of graft failure
- NASH patients have increased risk of cardiovascular disease and death
  - Shortened survival
- NASH progresses
  - Cryptogenic cirrhosis
  - Hepatocellular carcinoma (2.6%)
Presentation and Screening

Liver disease (hepatocellular, not biliary) is usually silent

- Most patients are asymptomatic
- ? Fatigue/malaise, occasional RUQ pain or HM

Liver disease is often an incidental finding – or picked up on screening

AAP recommends screening obese children (≥ 95% BMI) AND overwt (≥ 85% BMI) + risk:

- Check for dyslipidemia and NAFLD (screen with ALT)
- Consider checking vitamin D and insulin resistance
Diagnosis of NAFLD/NASH

- Labs
  - LFTs: Elevated transaminases
  - Labs to help rule out other liver diseases: Hep B, Hep C, Wilson’s, alpha-1 antitrypsin, autoimmune hepatitis, celiac disease
  - [Fasting insulin, glucose, HbA1C, lipids]

- Ultrasound
  - Suggestive if appearance is echogenic

- Liver biopsy (gold standard diagnosis)
Ultrasound: “Echogenic”

- Ultrasound has up to 85% sensitivity for detecting fatty liver
- Not specific (multiple other diseases can appear echogenic, eg hepatitis, cirrhosis, storage diseases...)

Hepatology 2011:54
What else causes fatty liver?

- Cystic Fibrosis
- FA oxidation disorders
- Peroxisomal/lysosomal
- Wilson’s disease
- Reye’s syndrome/mitochondriopathies
- LCAT deficiency
- Wolman’s disease
- Fatty liver of pregnancy
- Hepatitis C
- Alcohol
- Lipodystrophy
- Starvation
- TPN
- Abetalipoproteinemia
- Medications
What to know when you order the ultrasound

- **Benefits:**
  - Noninvasive, accessible, easy first step
  - Can assess spleen size and liver contour (? nodularity) and size
  - Rule out lesions/masses, GB or biliary disease

- “Consistent with” does not a diagnosis make
  - “Echogenic parenchyma, consistent with fatty liver disease”

- Ultrasound provides no measure of severity
  - No measure of fibrosis (unless there is portal hypertension and SM); does not differentiate simple steatosis vs. steatohepatitis

- Ultrasound is also unreliable to exclude fatty liver!
  - Transplant data: N=492 living donor transplants were done taking livers of patients who had normal ultrasounds and normal ALT and AST:
  - 18% had fatty liver disease

*Transplantation 2013; 95*
Liver biopsy: Non-alcoholic Steatohepatitis (NASH)

- Lipid globules, portal inflammation
- Portal fibrotic expansion
Liver biopsy: pros and cons

**Pros:**

- Only way to distinguish b/w steatosis, NASH, and fibrosis
- Gold standard for diagnosis
- Stage and Grade
  - Peds NAFLD histology score
- Can exclude other causes or additional disease (especially Autoimmune Hepatitis)
- [Reality check?: demonstrating end-organ damage.]  
  - Strengthening resolve of patients to follow treatment recommendation?

**Cons:**

- No specific treatment, so results do not provide a clinical benefit
- Risks of a procedure
  - Though small, it is still a procedure
  - 0-4.6% overall risk
  - Operator dependent
  - Highest risk in sickest patients (other diseases)
- ⇒ Benefits do not outweigh risks

**AASLD practice guidelines:** “Consider in patients at increased risk for NASH and fibrosis”  
(=Children, who are the most at risk for earlier, severe complications)
Liver biopsy procedure

- Not surgery
- Percutaneous
- Interventional radiologists perform ultrasound-guided needle biopsies:
  - ~no recovery time
- Gelfoam insertion at biopsy site can further reduce bleeding risk
- Risk of bleeding 0-4%
Screening negative, transaminases stable and <300

- **Weight Management**
  - Recommend Vitamin E (+/- fish oil)

  - Recheck labs q 3-6 months x 6 mo

  - Enzymes improved

  - Recheck labs q 3-6 months x 6 mo

  - Enzymes improved

  - Enzymes worsened

Abnormal screens, increasing trend of enzymes, or transaminases >300

- **Biopsy**

  - Recheck LFTS; send screening labs for other disease; u/s

  - Enzymes improved

  - Enzymes worsened

Follow…
Treatment of NASH

- “Is there a pill he can take???”
  - Meta analysis of medication trials: “No effective treatment”

- Treatment of insulin resistant state
  - Metformin; pioglitazone
    - No effect in placebo controlled multicenter trial

- Treatment of inflammatory component
  - Antioxidants: **vitamin E**
    - Insufficient vit E is associated with worse histology
    - Vit E (800 IU/D) => improvement of NASH on liver biopsy
    - Recommended to get liver biopsy before starting vitamin E

- **Gastric bypass?** Adjustable gastric banding?
  - Not enough data to recommend

- **Weight management!!!** Difficult: behavior change, family change, poor compliance, access issues
  - Exercise
  - Improved nutrition: Decreased high fructose corn syrup
  - Italian study: of n=84 children with NAFLD, >20% weight reduction in one year improved ALT and u/s-based evidence of steatosis

*JPGN 2012; 54, JAMA 2011; 305, Hepatology 2011, NEJM 2010; 362*
DHA for Fatty liver?

- **Abstract**: after 6 months on DHA supplementation, liver fat content diminished by u/s. ALT, TG, and insulin sensitivity improved
  - Biopsy improved as above after 16 months
- Pediatric clinical studies without biopsy also show improvement
- Large pediatric clinical trial underway…
- AASLD guidelines:
  - Omega 3 fatty acids are “helpful in treating dyslipidemia but there is not enough data yet regarding effect on NAFLD”
NASPGHAN patient education...

- Avoid sugary drinks
  - Limit to water and some skim milk
- Engage in 60 min activity daily
- Limit TV to <= 1 hour
- Make vegetables ½ of any meal plate
- Eat breakfast
Prognosis/complications

- NASH associated cirrhosis is now the 3rd most common reason for transplant (pediatric and adult)
  - Projected to be #1 by 2025
  - Last year a 21 yo required OLT for NASH

- Risk of increasing fibrosis associated with:
  - Higher level of ALT, a longer duration of ALT elevation, longstanding obesity, HTN, and presence of DM

- NAFLD in children is associated with significantly shorter survival compared with children of the same age and sex in the general population

- NAFLD in children may progress to cirrhosis and end-stage liver disease, with the consequent need for liver transplant
  - Transplant is not a guarantee of a cure, because NAFLD with severe NASH may recur in the allograft
Summary

- **Suggestive signs/symptoms:**
  - Central obesity, Acanthosis nigricans, HTN, insulin resistance
  - Family history of liver disease (even “alcoholic”!)

- Labs, ultrasound and often biopsy are used to assess for NASH and exclude other liver disease

- **Take home messages:**
  - Common, and becoming more common
  - Exacerbates other liver conditions
  - Improves with weight loss
  - May require transplantation (though usually not in childhood)