Nonalcoholic Fatty Liver Disease (NAFLD)
Outline of NAFLD Module

Obesity Epidemic
NAFLD Definition and Prevalence
NAFLD Presentation and Pathology
NAFLD Natural History
NAFLD Diagnosis
NAFLD Management
Obesity Epidemic
### Increased Prevalence of Extreme Obesity in Children

<table>
<thead>
<tr>
<th>BMI</th>
<th>Status</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 85th percentile</td>
<td>Overweight</td>
<td>32%</td>
</tr>
<tr>
<td>≥ 95th percentile</td>
<td>Obese</td>
<td>17%</td>
</tr>
<tr>
<td>≥ 99th percentile</td>
<td>Extremely Obese</td>
<td>4-8%</td>
</tr>
</tbody>
</table>

NAFLD: Definition and Prevalence
Prevalence of NAFLD

Excess fat in the liver = Steatosis

Steatosis without alcohol = NAFLD

~ 6 million children have NAFLD

Steatosis with inflammation/fibrosis = NASH
(Nonalcoholic steatohepatitis)

~ 10-30% may develop NASH

~ 7-10% may develop Cirrhosis and some possibly progress to HCC

NAFLD Prevalence in Adults

1988 to 1994
- 46.8% of all Chronic Liver Disease cases

1994 to 2004
- increased to 62.84%

2005 to 2008
- to 75.1%

NAFLD is the most common chronic liver disease in the world today!

Canada 35%
Italy ~20-25%
USA 31%
Russia ~30%

NAFLD: Presentation and Pathology
NAFLD: Signs/Symptoms

Nonspecific and often silent:
- Obesity (BMI >95% for age)
- Hepatomegaly
- RUQ discomfort
- Acanthosis nigricans
- Obesity comorbidities
  - Diabetes, Gallstones, Polycystic ovarian syndrome, Hypertension, Hyperlipidemia
Acanthosis Nigricans in Neck
Gross Liver Morphology

N - Normal liver
F - Fatty liver
NASH Histology

- Ballooning Degeneration
- Foci of lobular inflammation
NASH Histology-Fibrosis

Macrovesicular steatosis

Trichrome stain (blue) highlighting fibrosis
Increased Fructose Consumption Is Associated with Fibrosis Severity in Patients with Nonalcoholic Fatty Liver Disease

NIH-NASH Clinical Research Network Study

Adults drinking >7 servings of fructose rich beverages /week (sodas, kool-aid etc) had more severe fibrosis

The occurrence of the G allele of a lipid metabolism gene, PNPLA3, increased the risk of severe NAFLD.
NAFLD: Natural History
Natural History

Adults: 420 adults
NASH subjects had liver related death as 3rd leading cause vs. 13th in general population
- Increased heart related complications
- 5% developed cirrhosis

Pediatrics: 63 children
Retrospective study with small sample size
Needs further study

Long-Term Follow-up of Patients With NAFLD and Elevated Liver Enzymes

*Hepatology 2006;44:865-873.*

Mattias Ekstedt,¹ Lennart E. Franzén,² Ulrik L. Mathiesen,³ Lars Thorelius,⁴ Marika Holmqvist,⁵ Göran Bodemar,¹ and Stergios Kechagias⁶
NASH produces a significant increase in mortality
Clinical Vignette
# Pediatric Clinical Vignette: Progression of Fibrosis

<table>
<thead>
<tr>
<th></th>
<th>Patient A</th>
<th></th>
<th>Patient B</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Biopsy #1</td>
<td>Biopsy #2</td>
<td>Biopsy #1</td>
<td>Biopsy #2</td>
</tr>
<tr>
<td>Age</td>
<td>11</td>
<td>16</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.7</td>
<td>122.2</td>
<td>75.1</td>
<td>103.6</td>
</tr>
<tr>
<td>BMI</td>
<td>28.2</td>
<td>38.6</td>
<td>31.8</td>
<td>36.05</td>
</tr>
<tr>
<td>AST</td>
<td>59</td>
<td>114</td>
<td>112</td>
<td>256</td>
</tr>
<tr>
<td>ALT</td>
<td>134</td>
<td>172</td>
<td>240</td>
<td>390</td>
</tr>
<tr>
<td>GGT</td>
<td>73</td>
<td>105</td>
<td>97</td>
<td>89</td>
</tr>
<tr>
<td>Platelet count</td>
<td>355</td>
<td>252</td>
<td>262</td>
<td>239</td>
</tr>
<tr>
<td>NAFLD Activity Score</td>
<td>4/8</td>
<td>4/8</td>
<td>4/8</td>
<td>6/8</td>
</tr>
<tr>
<td>Fibrosis Stage</td>
<td>1c/4</td>
<td>3/4</td>
<td>1c/4</td>
<td>3/4</td>
</tr>
</tbody>
</table>

Progression of Fibrosis

Biopsy #1: Age 11 BMI 28

Stage 1c fibrosis

Biopsy #2: Age 16 BMI 38

Stage 3 "bridging" fibrosis
NAFLD: Diagnosis
Limitations of AST and ALT

Poor correlation with histology

Broad differential diagnosis

- Viral hepatitis
- Autoimmune hepatitis
- Wilson’s disease
- Alpha-1 antitrypsin
- Hemochromatosis
- Celiac disease
- Medication toxicity
- Genetic and metabolic disorders
NAFLD and ALT

The median upper limit of ALT at children's hospitals was 53 U/L while 95th percentile levels for ALT in healthy weight, metabolically normal, liver disease-free, NHANES pediatric participants were 25.8 U/L (boys) and 22.1 U/L (girls).

Serum alanine aminotransferase levels may decrease on placebo and is not a reliable measure of treatment response in NAFLD.

NAFLD and ALT

The median upper limit of ALT at 11 pediatric hospitals was 53 U/L while Schiwammer et al. used levels for ALT in healthy, metabolically normal children. NHANES pediatric disease-free, participants were 25.8 U/L (boys) and 22.1 U/L (girls).

Serum aminotransferase levels may be increased on placebo and is not a reliable measure of treatment response in NAFLD.

Ultrasound

Non-invasive
Cannot differentiate between NAFLD and NASH Guidelines

- Liver-kidney contrast and vascular blurring for fatty liver
- Sensitivity 83%, Specificity 100%, Accuracy of 96%

Ultrasound

Non-invasive

Non-alcoholic fatty liver disease in the Asia-Pacific region:
Definitions and overview of proposed guidelines

Shivakumar Chitturi, Geoffrey C Farrell, Etsuko Hashimoto, Toshiji Saibara, George KK Lau,
José D Sollano and the Asia-Pacific Working Party on NAFLD


Guidelines

- Liver-kidney contrast and vascular blurring for fatty liver
- Sensitivity 83%, Specificity 100%, Accuracy of 96%

When to Refer to GI?

- BMI > 95% for age
  - Ultrasound to check for steatosis
  - Check liver enzymes

- Steatosis and elevated AST/ALT
  - If persistently elevated > 2ULN for 3 months
  - Refer to Pediatric Gastroenterologist for further work up
MR/CT

• Pros:
  – Can identify fatty liver accurately
  – Can provide quantitative estimate of fat in liver

• Cons
  – Expensive
  – Cannot differentiate between NAFLD and NASH
A Combination of the Pediatric NAFLD Fibrosis Index and Enhanced Liver Fibrosis Test Identifies Children With Fibrosis

- Pediatric NAFLD Fibrosis Index was based on
  - age,
  - waist circumference,
  - and levels of triglycerides

- The Enhanced Liver Fibrosis test was based on
  - hyaluronic acid,
  - aminoterminal propeptide of type III collagen,
  - and tissue inhibitor of metalloproteinase-1

*Combining PNFI and ELF gave a better ROC-AUC*
Liver Biopsy

Current Gold Standard
Persistent elevated enzymes >2 ULN

Limitations
Invasive
Sampling error
Liver Biopsy

Current Gold Standard
Persistent elevated enzymes >2 ULN

Histopathologic Variability Between the Right and Left Lobes of the Liver in Morbidly Obese Patients Undergoing Roux-en-Y Bypass

STEVEN P. LARSON,* STEVEN P. BOWERS,‡ NICOLE A. PALEKAR,* JOHN A. WARD,§ JOSEPH P. PULCINI,‖
AND STEPHEN A. HARRISON‖

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2007;5:1329–1332
Features of Pediatric NASH

Pediatric

Portal inflammation (minimal or no lobular)

Adult

More severe ballooning

Portal and periportal fibrosis

Sinusoidal Fibrosis

NAFLD: Management
Management: Lifestyle Modification

Lifestyle intervention for non-alcoholic fatty liver disease: prospective cohort study of its efficacy and factors related to improvement

- Recommended changes:
  - Increased physical activity
  - Limit screen time
  - Behavioral Counseling
  - Increase family time and interaction

Management: Dietary Changes

- Recommended changes:
  - Increase fruit and vegetable intake
  - Decrease sugar sweetened beverage intake
  - Reduce take out and fast food meals
  - Avoid hepatotoxins (Especially alcohol in teens)
Management: Medications

- Treatment of Nonalcoholic Fatty Liver Disease in Children (TONIC)
  - Randomized 180 children to Metformin vs. Vitamin E vs. placebo
  - Results:
    - Significant improvement in resolution of NASH and improvement in NAFLD activity scores as seen with Vitamin E relative to placebo.
    - No effect of metformin.
    - Vitamin E as effective in resolving NASH in children as it is in resolving NASH in adults

Management: Bariatric Surgery

Stringent Criteria:

- 6 months prior non-surgical weight management
- Extremely obese (BMI 40 or greater)
- When adult height reached
Take Home Points (1/2)

- Pediatric NAFLD is a global epidemic
- NASH has a worse prognosis than steatosis alone
- ALT does not correlate well with disease
- The gold standard for diagnosis is liver biopsy
Take Home Points (2/2)

• Weight loss is the only long-term solution
• Protect your liver
  • Hepatitis A and B Vaccination
  • Avoid alcohol and other hepatotoxins
• Vitamin E is appropriate for biopsy-proven NASH in those who have had a biopsy