Nonalcoholic Fatty Liver Disease in Children: Typical and Atypical

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Disclosure
Naim Alkhouri, MD discloses the following relationships with commercial companies:
Membership in the Speakers’ Bureau for Alexion and Intercept.

Introduction

Learning Objectives
At the end of this presentation the participant will be able to:
1. Discuss the natural history of fatty liver disease in children and young adults.
2. Summarize the work up for a child with NAFLD.
3. Discuss treatment options for NAFLD.

Obesity and Adipose Tissue

- Simple Steatosis (NAFL)
- NASH/ Fibrosis
- Cirrhosis

Liver related morbidity and mortality

- Steatosis 10-20%
- NASH/ Fibrosis 10-20%
- Cirrhosis
**Pediatric Grand Rounds - UT Health San Antonio**

**Lipotoxicity**


**Disease Progression to NASH**


**NAFLD Prevalence**

- **Adults**
  - Overall: ~30%
  - Obese: ~50-70%
  - Severely Obese: 85%
  - DM2: ~65-75%
- **Children**
  - Overall: ~10%
  - 15-19 years: ~17%
  - Obese: ~50%


**Young Kids, Old Bodies**

Obesity is turning a generation of children into biological adults, ageing them before their time

**Natural History of NAFLD in Children**

A hospital-based cohort study

n = 66 children with NAFLD, follow up for up to 20 years

2 patients developed NASH-cirrhosis that required LT at 20 and 25 years

Feldstein et al. Gastroenterology 2009

**Frequency of NASH as a Cause of Liver Transplantation (LT) in Adults**

Charlton et al. Gastroenterology 2011;141:1249
**Screening for NAFLD: Pediatric Practice Guidelines**

- AAP:
  - Biannual screening with ALT measurement starting at 10 years of age for children with:
    - BMI ≥ 95th percentile.
    - BMI of 85-94th percentile with other risk factors.

- ESPGHAN:
  - Abdominal US and liver function tests should be performed in all obese children.

**Ultrasonography for NAFLD**

*US Cannot Stage the Severity of Fibrosis in Patients with NAFLD*

- Sensitivity (%)
  - 5-9%: 0
  - 10-19%: 10
  - 20-29%: 20
  - ≥ 30%: 30

**Liver Biopsy: Easier Said than Done**

- NAFLD affects 1/10 children
- 5 million American Children have NAFLD
- 5 million liver biopsies!!!
Staging the Severity of Fibrosis in NAFLD: VCTE

Actuator

VCTE + CAP: A Powerful Tool

Case Presentation
- 17 year female referred to the Metabolic Liver Center.
- Elevated ALT (87 U/L)
- Fatty infiltration of the liver on US.
- Weight: 338 lbs.
- BMI: 62 kg/m² (99.8th%)

Assessment of the Child with Suspected NAFLD
- 1. Rule out other etiologies for elevated liver enzymes/ fatty infiltration of the liver.
- 2. Evaluate for co-morbidities/ extra-hepatic manifestations of NAFLD.
- 3. Determine the severity of NAFLD
  - Presence of NASH
  - Presence of liver fibrosis

1. Rule out other etiologies

   Other conditions that cause fatty liver
   - Excessive alcohol consumption
   - Malnutrition
   - Medications
   - Parenteral nutrition
   - Confining liver diseases
     - Hepatitis B (hepatitis B surface antigen, hepatitis B core antibody)
     - Hepatitis C (hepatitis C antibody)
     - α1 Antitrypsin deficiency (α1-antitrypsin level)
     - Wilson disease (Ceruloplasmin)
     - Haemochromatosis (Ferritin/TIBC/iron)
     - Primary biliary cirrhosis (anti-mitochondrial antibody)
     - Autoimmune (Anti-nuclear antibodies, anti-liver- kidney microsomal antibodies type 1, anti-smooth muscle antibody)

   Mencine A and Lavine J. Nat Rev Gastroenterol Hepatol. 2015

2. Evaluate for co-morbidities
Laboratory Assessment for Children with NAFLD

Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C</td>
<td>6.2% (&lt;5.7)</td>
</tr>
<tr>
<td>Fasting Insulin</td>
<td>52 μU/mL (&lt; 20)</td>
</tr>
<tr>
<td>TG</td>
<td>228 mg/dL (&lt;150)</td>
</tr>
<tr>
<td>HDL</td>
<td>36 mg/dL (&gt; 40)</td>
</tr>
<tr>
<td>Vitamin D 25 OH</td>
<td>16.5 ng/mL (&gt;30)</td>
</tr>
<tr>
<td>PSG + OSA</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>87 U/L (0-45)</td>
</tr>
</tbody>
</table>

Liver US: Fatty infiltration

3. Determine the Severity of NAFLD

- VCTE: Liver stiffness at 12 kPa → consistent with F3 fibrosis (bridging).
- Liver biopsy: NASH with bridging fibrosis.

NAFLD Treatment

PRE-DIABETES

- Simple Steatosis (NAFL)
- NASH/Fibrosis
- Cirrhosis

DIABETES COMPLICATIONS

- Diabetes
- Gastrointestinal bleeding
- Nephropathy
- Neurological complications
- Cardiovascular disease
- Complications

TONIC: Vitamin E or Metformin for Treatment of Pediatric NAFLD

- Double-blind, placebo-controlled, randomized, multicenter Phase II trial
- 81% boys, 61% Hispanic, 42% with baseline NASH, mean BMI 34 kg/m², mean baseline ALT 125 U/L
- Children aged 8 to 17 years with NAFLD, no diabetes or cirrhosis (N = 173)

Primary Endpoint: Reduction in ALT at Week 96

- No significant difference between vitamin E and placebo ($P = .07$) or metformin and placebo ($P = .40$)

Secondary Endpoint: Resolution of Definite or Borderline NASH at Week 96

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vitamin E (n = 43)</th>
<th>Placebo (n = 38)</th>
<th>Metformin (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolved, %</td>
<td>58</td>
<td>28</td>
<td>41</td>
</tr>
<tr>
<td>P value vs placebo</td>
<td>.006</td>
<td>--</td>
<td>.23</td>
</tr>
</tbody>
</table>

The Race to Cure NASH:
Two Medications in Phase III RTCS

- Obeticholic acid (OCA):
  - FXR agonist
  - Anti-fibrotic

- Elafibranor:
  - PPAR $\alpha$-δ agonist
  - Decrease LDL, increase HDL, favorable metabolic profile

The FLINT trial

- Obeticholic acid (OCA), 25 mg orally daily vs placebo
- Inclusion: adults with NASH on biopsy, NAS $\geq$ 4
- Exclusion: cirrhosis
- N = 283 patients randomized at 8 clinical centers
- 72 weeks of treatment
- Biopsy $\leq$ 3 mo. before treatment and after 72 weeks
- Primary endpoint:
  - Improvement in NAFLD activity score $\geq$ 2 pts with no worsening of fibrosis
PPAR α-δ Agonist: A Novel Treatment for NAFLD

An international, phase 2 RCT of the dual PPAR α-δ agonist Elafibranor in NASH: GOLDEN

Primary Endpoint: Reversal of NASH

LEAN: Liraglutide for 48 Wks

NASH Therapies in Development

Take Home Message

- NAFLD is potentially serious even during childhood and early adulthood.
- Work up:
  - Rule out other etiologies for CLD
  - Assess for co-morbidities
  - Assess severity
- NASH-specific therapy are emerging rapidly.
Atypical NASH: Case Presentation

- 17 year female referred to the Metabolic Liver Center.
- Elevated ALT (87 U/L)
- Fatty infiltration of the liver on US.
- Weight: 138 lbs.
- BMI: 22.3 kg/m2

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
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<tbody>
<tr>
<td>HbA1C</td>
<td>4.8% (&lt;5.7)</td>
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<tr>
<td>Fasting Insulin</td>
<td>12 μU/mL (&lt; 20)</td>
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<tr>
<td>TG</td>
<td>228 mg/dL (&lt;150)</td>
</tr>
<tr>
<td>HDL</td>
<td>26 mg/dL (&gt; 40)</td>
</tr>
<tr>
<td>LDL</td>
<td>210 mg/dL (&lt; 110)</td>
</tr>
<tr>
<td>Platelet</td>
<td>135K (&gt; 150K)</td>
</tr>
<tr>
<td>ALT</td>
<td>87 U/L (0-45)</td>
</tr>
<tr>
<td>Liver US</td>
<td>Fatty infiltration, massive hepatomegaly</td>
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</tbody>
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