NASH in Children

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History of NASH

- 1980- A pattern of liver injury resembling alcoholic hepatitis in patients with no history of drinking is described: non-alcoholic steatohepatitis, NASH (Ludwig)
- 1983- NASH is described in children (Moran)
- 1990- Cirrhosis in NASH is described
- 2002- NASH Clinical Research Network begins

Some slides care of J. Molleston
Definitions

- **NAFLD** Non-Alcoholic Fatty Liver Disease:
  - Simple steatosis: Fat, no inflammation

- **NASH**: Fat, accompanied by inflammation and evidence of hepatocyte injury

- **Cirrhosis**: Bridging fibrosis with regenerative nodules, possibly without fat

* No history of significant alcohol consumption
  - < 2 drinks/day in women, < 3 drinks/day in men
Stages of Fatty Liver Disorders

Fatty Liver

16-35% of Western Population
9.6% of Children
1/3 of Obese Children

16%

Steatohepatitis

25%

Steatohepatitis with Fibrosis

20%

Steatohepatitis with Cirrhosis

30%

25%

ESLD

Liver Cancer
Non-NASH Diseases that Can Cause Fatty Liver

- Wilson’s Disease
- Metabolic Disorders including mitochondrial disease
- Hepatitis C
- Cystic Fibrosis
- Drugs: Steroids, tamoxifen, methotrexate, amiodarone
- TPN, starvation
Conditions Associated with NAFLD

- Obesity
- Diabetes
- Metabolic syndrome
- Polycystic Ovary Syndrome
- Hyperlipidemia
NAFLD: Adult Epidemiology

- Prevalence estimate 13-26%
- MRS prevalence 34%
- Ultrasound prevalence:
  - 16% of normal weight persons
  - 62% of diabetics
  - 76% patients with BMI >30
- Autopsy prevalence:
  - 2.7% of those with normal weight
  - 18.5% of obese persons
- Abnormal ALT 2.5-5.5% of adults in US

Pediatric NASH Epidemiology

- Obesity (90%), Acanthosis nigricans, hepatomegaly
- Boys 40% > Girls
- Ages 2-17 years (avg 12 years)
- 25-30% abdominal pain
- Autopsy data:
  - Fatty liver in 9.6% of 742 pediatric autopsies
  - Fatty liver: Hispanic 12%, Asian 10.2%, White 8.6%, African-American 1.5%
  - Fatty liver in 38% of obese children
  - NASH in 3% (23% of the subjects with fatty liver)

NASH Pathophysiology: “2-Hit Theory”

First hit: Hepatic steatosis due to insulin resistance

- lipogenesis
- TG
- Glucose
- Insulin
- Fatty acid influx into liver
- Fat oxidation
NASH Pathophysiology: “2-Hit Theory”

- First hit: Hepatic steatosis is caused by insulin resistance:
  - Leptin may stimulate inflammation, fat storage
  - Adiponectin is anti-inflammatory, anti-steatotic
Recent Bench Data: Insulin Resistance Underlies NASH

- 2 rat strains: One strain obese/insulin-resistant, one not
- NASH induced in rats via choline deficient diet
- Non insulin-resistant rats were resistant to NASH
- NASH improved only when obese/IR rats were treated with pioglitazone and increased adiponectin

NASH Pathophysicsiology: 2nd Hit

- Oxidative stress
- Inflammatory mediators/cytokines
- Lipotoxicity: Direct toxicity to hepatocytes (lipid peroxidation)
- Mitochondrial permeability
- Stellate cell activation/mediators of fibrosis
- Other factors

Significant Histologic Abnormalities in Children with ALT < 60

- Steatosis: > Grade 2
- Lobular Inflammation: > Grade 2

Fibrosis in Children with NASH and ALT<60

Stage 0 or 1 fibrosis: 87%

Stage 2 fibrosis: 3% (3% with Bridging fibrosis)

Cirrhosis: 6%

Molleston: NASPGHAN Abstract 2009.
Imaging of NAFLD

CT Fatty Liver

US Fatty Liver

Images from Medscape
Histology of NASH

- Ballooning degeneration
- Mallory’s hyalin
Progressive Histology of NASH

NAFLD Disease Progression
Types of non-alcoholic fatty liver

A. Type I
Fat alone

B. Type II
Fat alone ± inflammation
Benign

C. Type III
Fat alone ± inflammation ± ballooning degeneration ± Mallory Bodies
Progressive

D. Type IV
Steatosis
Fibrosis
CV

Fibrosis
NASH Cirrhosis
**Adult NASH:** Centrilobular steatosis, ballooning, Mallory bodies, sinusoidal fibrosis

**Pediatric NASH:** Severe diffuse steatosis, periportal inflammation and fibrosis

Patton. JPN 2006;43:413.
Natural History of NAFLD

- 420 adults in USA diagnosed with NAFLD
- 7.6 (0.1 - 23.5) year follow-up
- 22% developed diabetes
- 5% with cirrhosis
- 3.1% with liver-related complications (including one transplant and 2 HCC)
- Among deaths, 13% due to liver disease, 25% due to CAD

Gastroenterology 2005;129:113

- RR of Liver Cancer in men BMI>35 is 4.52 (Prostate = 1.34; All cancers = 1.52)

N Engl J Med 2003;348:1625-1638
Mortality in Adults with NASH

A Kaplan-Meier survival curve showing the survival rates over time. The expected survival rate is compared with the observed survival rate. The p-value is 0.03.

Natural History of NASH in Children

- 66 Children followed for up to 20 years
- 4/66 (6%) developed diabetes in 4-11 years
- 4/5 children with multiple liver biopsies showed progression of fibrosis
- 2 children died
- 2 children were transplanted for decompensated cirrhosis (both had recurrent NASH in the graft)
- Standardized mortality ratio 13.6

Feldstein et al, Gut, 2009
NASH Comorbidities

- Obstructive sleep apnea may correlate with ALT
- NASH is associated with increased risk of cardiovascular disease in adults
- NASH is associated with higher carotid artery intimal thickness in children
- NAFLD is associated with increased risk of metabolic syndrome in children

## Proposed NASH Causes and Treatments

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>★ Diet, exercise</td>
</tr>
<tr>
<td>Nutritional deficiencies</td>
<td>• Increase vitamins/fiber</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>★ Metformin, pioglitazone</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>★ Antioxidants</td>
</tr>
<tr>
<td>Cytokines, adipokines</td>
<td>• Anticytokine therapy</td>
</tr>
<tr>
<td>Bacterial overgrowth</td>
<td>• Probiotics/antibiotics</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>• Antihyperlipidemics</td>
</tr>
</tbody>
</table>

Adapted from NEJM 2006;355(22):2361. (commentary)
NASH Treatment
Lifestyle/Weight Loss

- Studies in adults:
  - 4 studies (40 subjects) of calorie restriction
  - 10 studies (626 subjects) of diet + exercise
- Beneficial effects have been seen on ALT, insulin resistance, liver fat, and inflammation/fibrosis
Treatment of Adult NASH

Metformin

- RCT in 110 adults with NASH:
  - 55 treated with metformin 1g bid
  - 55 treated with either vitamin E or diet
- ALT improved in all groups, especially metformin
- In metformin patients, improvement in fat, inflammation, and fibrosis on biopsy

Treatment of Adult NASH

Pioglitazone

- 55 adults with insulin resistance and NASH
- RCT 6 months:
  - hypocaloric diet + pioglitazone
  - hypocaloric diet + placebo

<table>
<thead>
<tr>
<th>Pioglitazone</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ ALT:</td>
<td>58%</td>
</tr>
<tr>
<td>↓ liver fat:</td>
<td>54%</td>
</tr>
</tbody>
</table>

- Improved inflammation but not fibrosis

Belfort et al, NEJM 2006;355(22):2297.
Improvement in ALT in Adult NASH on Pioglitazone

Belfort. NEJM 2006;355(22):2297.
## Summary of Adult Clinical Studies Regarding TZDs and NASH

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>N</th>
<th>Design</th>
<th>Agent</th>
<th>Duration</th>
<th>Liver Biopsy</th>
<th>Amino-transferases</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caldwell, et al. 2001</td>
<td>10</td>
<td>Open label</td>
<td>Troglitazone</td>
<td>3-6 Months</td>
<td>5</td>
<td>Improved</td>
<td>Improved mild inflammation</td>
</tr>
<tr>
<td>Neuschwander-Tetri, et al. 2003</td>
<td>30</td>
<td>Open label</td>
<td>Rosiglitazone</td>
<td>48 Weeks</td>
<td>22</td>
<td>Improved</td>
<td>Improved steatosis and inflammation</td>
</tr>
<tr>
<td>Promrat, et al. 2004</td>
<td>18</td>
<td>Open label</td>
<td>Pioglitazone</td>
<td>48 Weeks</td>
<td>18</td>
<td>Improved</td>
<td>Improved steatosis, inflammation, and fibrosis</td>
</tr>
<tr>
<td>Sanyal, et al. 2004</td>
<td>21</td>
<td>RCT</td>
<td>Pioglitazone</td>
<td>6 Months</td>
<td>?</td>
<td>Improved</td>
<td>Improved steatosis, inflammation and fibrosis</td>
</tr>
<tr>
<td>Belfort, et al. 2006</td>
<td>55</td>
<td>RCT</td>
<td>Pioglitazone</td>
<td>6 Months</td>
<td>47</td>
<td>Improved</td>
<td>Improved steatosis and inflammation</td>
</tr>
</tbody>
</table>

Adult NASH PIVENS Trial: Pioglitazone vs Vitamin E vs Placebo

- 247 Adult patients randomized to Pioglitazone or Vitamin E or placebo for 2 years in NASH CRN
- Histologic improvement endpoint reached by:
  - 43% of Vitamin E
  - 34% of Pioglitazone
  - 19% of placebo
- ↓ steatosis, inflammation, ALT in Pioglitazone and Vitamin E group
- Ave weight gain: Pioglitazone- 5 kg
  - Vitamin E- 0.4 kg
  - Placebo- 0.8 kg

Hepatology 50(4), 2009.
Effects of Bariatric Surgery on NASH: A Meta-analysis

- 15 Studies, 766 paired liver biopsies
- Reduction in BMI of 19% to 42%
- Steatosis improved 92%
- Steatohepatitis improved 81%
- Fibrosis improved 66%
- Complete resolution of NASH 70%

NASH Treatment in Children: Metformin

- Open-label pilot study: 10 children NASH and elevated ALT; Treatment 6 months
  - Mean ALT 184 → 98
  - MRI Liver fat 30% → 23%
  - HRQOL improved
  - Weight decreased by 1kg, BMI by 1.6 (80% of subjects didn’t lose weight)

Open-label Pilot study in 11 children with NASH

- Vitamin E 400-1200 IU, for 2-4 months
- All 11 normalized ALT, without weight loss

Pediatric NASH TONIC Trial
Metformin vs Vit E vs Placebo

- Inclusion criteria:
  - Ages 8-18 years
  - Liver biopsy showing NASH within last 6 months
  - ALT >60 IU/L

- Outcomes:
  - ALT
  - Biopsy
  - HRQOL, etc, etc
Summary

- NASH is a potentially serious disease
- Diet and exercise resulting in slow steady weight loss should, for many reasons, be recommended and can improve NASH
- Vitamin E appears to be helpful for the treatment of NASH in adults
- Insulin sensitizers like metformin and pioglitazone may be helpful for treatment of NASH
- Monitor for co-morbidities