Overview of “Common” Pediatric Metabolic Liver Diseases

Philip Rosenthal, M.D.
Professor of Pediatrics & Surgery
University of California, San Francisco
Conflict of Interest Disclosures for Philip Rosenthal, MD
All conflicts have been resolved

<table>
<thead>
<tr>
<th>Category</th>
<th>Disclosures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td>Roche, Gilead, Bristol Myers Squibb, Vertex, NIH</td>
</tr>
<tr>
<td>Consultant</td>
<td>Hyperion, General Electric, Gilead, Abbvie</td>
</tr>
<tr>
<td>Speakers Bureau</td>
<td>Nothing to disclose</td>
</tr>
<tr>
<td>Stock Shareholder</td>
<td>Nothing to disclose</td>
</tr>
<tr>
<td>Employee</td>
<td>Nothing to disclose</td>
</tr>
<tr>
<td>Other (identify)</td>
<td>Nothing to disclose</td>
</tr>
</tbody>
</table>
Unapproved or Off Label Disclosures for Philip Rosenthal, MD

Presenter: Philip Rosenthal, MD has documented that his/her presentation will not involve discussion of unapproved or off-label, experimental or investigational use.
TOPICS

• A1AT-chaperones/siRNA
• Alagille Syndrome
• Wilson Disease
• Pediatric NASH
A1AT Deficiency

- Autosomal recessive
- 1:1600 to 1:2000 live births
- The most common disease-causing alleles are PiZ (Glu342Lys) and PiS (Glu264Val)
- 11% of PiZ patients develop neonatal cholestasis, 25% progress to early liver failure, 25% go onto cirrhosis
- Because of abnormal protein folding, the Z protein has a propensity to polymerize within the endoplasmic reticulum (ER) of the hepatocyte, where it accumulates as the characteristic periodic acid Schiff–positive granules seen on light microscopy
A: Diastase-resistant inclusions are prevalent in hepatocytes but rare in carcinomatous nodule (*). (PAS+ stain after diastase treatment). B and C: Storage material in hepatocytes is demonstrable by peroxidase immunostain in paraffin section and fluorescein-conjugated antibody in frozen section. D: Alpha-1 Antitrypsin protein accumulates in endoplasmic reticulum of hepatocytes. (Electron Microscopy)
Cirrhosis in 13 month old child with ZZ phenotype
A1AT Liver Disease Therapy

• Liver transplant
• Chaperones
• MiRNA
Chaperone-mediated Autophagy
Chaperone Therapy Carbamazepine
Alagille Syndrome

• Genetic disorder that affects the liver, heart, kidney, eyes, bones
• Inherited in an autosomal dominant pattern
• Estimated prevalence is 1 in every 100,000 live births
• It is named for Daniel Alagille, a French pediatric hepatologist
Alagille Syndrome

Characteristic Facies

- Broad, prominent forehead
- Deep-set eyes
- Small, pointed chin
- Bulbous tip of nose
Alagille Syndrome

Butterfly vertebrae

Hemi-vertebrae
Alagille Syndrome

- Heart defects - peripheral pulmonic stenosis
- VSD
- Aortic stenosis
- Tetralogy of Fallot
- Xanthomas
Alagille Syndrome

Paucity of intrahepatic ducts

• Posterior embryotoxon
Alagille Syndrome

• Most cases of Alagille syndrome are caused by a mutation in the JAGGED1 (JAG1) gene
• In less than 1 percent of cases, a mutation in the NOTCH2 gene is the cause
Alagille Syndrome-Trials

- Evaluation of LUM001 in the Reduction of Pruritus in Alagille Syndrome (ITCH)
- Safety and Efficacy Study of LUM001 in the Treatment of Cholestatic Liver Disease in Patients With Alagille Syndrome (IMAGO)
- An Extension Study to Evaluate the Long-Term Safety and Durability of Effect of LUM001 in the Treatment of Cholestatic Liver Disease in Subjects With Alagille Syndrome (IMAGINE)
- LUM001 is an inhibitor of the apical sodium-dependent bile acid transporter (ASBT), which recycles intestinal bile acids back into the circulation
Wilson Disease

- In 1912, Dr. S.A. Kinnier Wilson described 4 patients with a profound movement disorder and cirrhosis of the liver
- The molecular basis of WD is now well understood, with mutations in the gene ATP7B being responsible for the failure of biliary excretion and incorporation of copper into ceruloplasmin
- The ATP7B gene encodes for an ATP-dependent copper transporter with 8 transmembrane domains, which is active in the trans-Golgi
- Defects in the WD protein lead to accumulation of copper in the liver and subsequently in the brain, cornea, kidney, and other tissues
Wilson Disease

2012 – centenary of the first publication on Wilson’s disease

Samuel Alexander Kinnier Wilson (1878-1937)

Kayser Fleischer Ring
Wilson Disease

- WD disease may present clinically in a number of ways
- Pediatric presentations of WD are typically hepatic, including asymptomatic disease detected on routine physical examination, chronic hepatitis, cirrhosis, and fulminant hepatic failure
- Another important presentation results from screening the premorbid sibling of an affected individual
- Neurological presentations are predominantly seen in adults but can occur in adolescents and feature a progressive movement disorder with dysarthria, dysphagia, apraxia, and tremor
- Neurological presentations also include psychiatric manifestations in approximately one-third of patients
  - These manifestations may include diminished performance at work or school, depression, mood swings, and frank psychosis
Wilson Disease

- WD has been described in all ethnic groups and has an overall estimated incidence of 1 in 30,000-50,000 births, but in some ethnic groups, the incidence may be much higher, particularly in Sardinia, where 10-12 new cases are reported per year.
- Mutational analysis approach estimates the incidence in Caucasians in the United States as 1 in 55,000.
- There have been >200 mutations described, and although some mutations are more common in a particular ethnic or geographical population, there is no “common” mutation.
Wilson Disease

- Commonly the diagnosis is straightforward with the presence of Kayser-Fleischer rings, a low serum ceruloplasmin level, increased urinary excretion of copper, and elevated liver copper on biopsy
- A diagnosis of WD is unlikely to occur without clinical suspicion and appropriately directed investigation
- All standard tests used to secure a diagnosis of WD have their drawbacks, and results of these tests may misdirect the diagnosis either away from a true diagnosis of WD, such as a normal level of ceruloplasmin and absence of Kayser-Fleisher rings, or toward WD because of a high liver copper level
- Because the diagnosis can be so challenging, an expert panel developed a diagnostic scoring system that has come to be known as the Leipzig criteria
- Only the demonstration of 2 disease-causing mutations in ATP7B can absolutely secure the diagnosis
Wilson’s Disease Scoring System


- Kayser-Fleischer rings*
  - Present
  - Absent
- Neurologic symptoms***
  - Severe
  - Mild
  - Absent
  **or typical abnormalities at brain magnetic resonance imaging.
- Serum ceruloplasmin*
  - Normal (>0.2 g/L)
  - 0.1-0.2 g/L
  - <0.1 g/L
- Coombs-negative hemolytic anemia*
  - Present
  - Absent
- Liver copper (in the absence of cholestasis)*
  - >5x ULN (>4 μmol/g)
  - 0.8-4 μmol/g
  - Normal (<0.8 μmol/g)
- Rhodanine-positive granules*
- Urinary copper (in the absence of acute hepatitis)*
  - Normal
  - 1-2x ULN
  - >2x ULN
- Mutation analysis*
  - On both chromosomes detected
  - On 1 chromosome detected
  - No mutations detected
- Score
Wilson Disease Therapy

- Chelation therapy with D-penicillamine, trientine, or ammonium tetrathiomolybdate, with or without zinc salts, introduced in a timely manner has been shown to be effective in preventing progression of WD and in many cases may lead to resolution of symptoms.
- However, medical treatment cannot be expected to reverse decompensated cirrhosis, fulminant liver failure, or established neurological injury.
- Choice of medical therapy is provider-dependent and has not been comparatively analyzed.
- LT before the onset of extrahepatic features of WD cures the metabolic defect.
- However, medical therapy is highly effective, and therefore only those patients who have progressive liver disease despite chelation therapy should be considered for transplantation.
Definitions:

- Non-alcoholic fatty liver disease (NAFLD):
  - Hepatic steatosis, by imaging or histology
  - Diagnosis of exclusion
  - Includes entire disease spectrum:
    - Non-alcoholic fatty liver disease (NAFLD):
      - hepatic steatosis
      - WITHOUT hepatocyte injury
      - WITHOUT fibrosis
    - Non-alcoholic steatohepatitis (NASH):
      - hepatic steatosis
      - + inflammation/ballooning
      - +/- fibrosis
      - Can progress to cirrhosis
Histology of NASH
NAFLD/NASH “Progression”
Pediatric NAFLD: Type 1 vs. Type 2

• **Type 1 NAFLD:**
  - “Adult-type”
  - Zone 3 steatosis

• **Type 2 NAFLD:**
  - ?Unique to children
  - Zone 1 steatosis
  - No ballooning
  - Portal inflammation/fibrosis

Loomba et al. HEPATOLOGY 2009;50:1282-1293
Kids are not just small adults . . .

“Type 2” NASH

NAFLD Pathogenesis

Two-hit hypothesis

1. Chronic ethanol consumption
   - ↑NADH/NAD⁺ & ↓AMPK, ↑SREBP
   - Hepatic Steatosis
   - Environmental toxins, ROS/RNS, cytokines, mitochondrial damage
   - "1st Hit"

2. Obesity/Cardiometabolic syndrome
   - Insulin resistance
   - Hepatic Steatosis
   - "2nd Hit"

Lipotoxicity hypothesis

- Adipose lipolysis
- Circulating fatty acids
- De novo lipogenesis
- Hepatocyte free fatty acid flux
- ROS
- Oxidant stress
- Elimination by antioxidants

Lipotoxic intermediates:
- Phosphatic acid
- Lyso phosphatic acid
- Lyso phosphatidyl choline
- Caramides
- Diacylglycerols
- Others

- ER stress
- Inflammation
- Apoptosis
- Necrosis

ASH/NASH

Mantena SK et al. 2008
Bass NM. Hepatology 2010
Is NAFLD really a problem in kids?

- Most common pediatric chronic liver disease in North America
- 2-9% of all U.S. adolescents
- 20% of U.S. obese adolescents
- Rates in younger children unknown
Natural history of NAFLD

- Not well understood
- In adults, NASH associated with:
  - Increased overall mortality risk
    - Leading cause of death: cardiovascular disease
    - Increased liver-mortality rate
  - NASH cirrhosis: Increased HCC risk
- In children: 1 retrospective single center study
  - 66 children
  - 5 with serial biopsies, 4 with fibrosis progression
The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association

Naga Chalasani, MD, FACP, Zobair Younossi, MD, FACP, Joel E. Lavine, MD, PhD, Anna Mac Diehl, MD, Elizabeth M. Brunt, MD, Kenneth Choi, MD, Michael Charlton, MD, and Anna J. Samel, MD

Consensus Statement

Diagnosis of Nonalcoholic Fatty Liver Disease in Children and Adolescents: Position Paper of the ESPGHAN Hepatology Committee

*Pietro Vajro, †Selvaggia Lenta, ‡Piotr Socha, †Anil Dhawan, †Patrick McKiernan, †Ulrich Baumann, **Ozlem Durmaz, ††Florence Lacaille, †††Valerie McLin, and †Valerio Nobili
AASLD/AGA/ACG grading

- **Strength of Recommendation**: factors include evidence quality, importance to patient outcomes, and cost
  1. STRONG
  2. WEAK

- **Quality of Evidence**
  - High (A): Further research unlikely to change confidence in the estimate of the clinical effect
  - Moderate (B): Further research may change confidence in estimate of the clinical effect
  - Low (C): Further research very likely to impact confidence on the estimate of clinical effect
AAP Guidelines for NAFLD Screening

• Starting at 10 years of age, every 2 years
• AST/ALT in pediatric patients with:
  – BMI $>$ 85$^{th}$ percentile for age/gender WITH risk factors OR
  – BMI $>$ 95$^{th}$ percentile for age/gender, regardless of risk factors
• Risk factors:
  – Family history of obesity-related diseases, including hypertension, early cardiovascular deaths, and strokes
  – Patient history of elevated blood pressure, hyperlipidemia, or tobacco use.

AASLD: NAFLD screening?

• Not recommended in adult primary care clinics or high-risk specialty clinics (diabetes, obesity) (1, B)

• Not recommended in overweight/obese children:
  – “Due to a paucity of evidence, a formal recommendation cannot be made with regards to screening for NAFLD in overweight and obese children despite a recent expert committee recommendation for biannual screening.” (1, B)

• Not recommended for family members of people with NAFLD or NASH (1, B)
  – 18% of NASH patients have a first degree relative with NASH
What are “normal” LFTs?

Figure 1. Reference ranges for serum alanine aminotransferase (ALT) reported by the 11 Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) laboratories. The bars indicate the reference ranges; the upper limit for women varied from 31 U/L in laboratory B to 55 U/L in laboratory E; the upper limit for men varied from 35 U/L in laboratory A to 79 U/L in laboratory K. The lower limit ranged from 0 to 12 U/L. To convert ALT to microkatal per liter, multiply by 0.0167.

What are “normal” LFTS?

- Screening ALT for Elevation in Today’s Youth (SAFETY)
- U.S. children’s hospitals:
  - ALT upper limit of normal: median (range)
    - ALL: 53 (30-90)
    - BOYS: 50 (30-70)
    - GIRLS: 40 (29-65)
- NHANES: 12-17 yrs w/o liver disease
  - 95th percentile ALT:
    - BOYS: 25.8 U/L
    - GIRLS: 22.1 U/L

When to biopsy adults for NAFLD?

• “Should be considered in patients with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis” (1, B)
  - Metabolic syndrome
  - NAFLD Fibrosis Score

• “Patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and co-existing chronic liver diseases cannot be excluded” (1, B)
When to biopsy children for NAFLD?

AASLD:
- “where the diagnosis of NAFLD is unclear”
- “where there is possibility of multiple diagnoses”
- “before starting potentially hepatotoxic medications”
- “prior to starting pharmacologic therapy for NASH”

ESPGHAN:
- “to exclude other treatable disease”
- “in cases of clinically suspected advanced liver disease”
- “before pharmacologic/surgical treatment”
- “as part of a structured intervention protocol or clinical research trial”
- “no present consensus or evidence base to formulate guidelines”
Approach to NAFLD diagnosis and management (ESPGHAN)

Children 3-10 y (NAFLD less probable)
- NAFLD diagnosis should be based after exclusions of viral, toxic, metabolic (eg. WD), systemic causes (eg. CD) workup
  - If negative or inconclusive

Children >10 y (NAFLD more probable)
- If central obesity, IR and no clinical signs of progressive liver disease
  - Trial of weight reduction and lifestyle changes for 3-6 months
    - If persistent hypertransaminasemia or hyperechogenicity at US
      - Perform laboratory workup of exclusion of other causes
        - If sustained hypertransaminasemia or hyperechogenicity at US
          - Consider early liver biopsy
    - Family history of NASH
      - Hepatosplenomegaly
      - Comorbidities
      - Hypothalamic
      - Expansive processes
      - Marked hypertransaminasemia
      - Elevated fibrosis
      - Serum markers
      - Consider liver biopsy

Consider early liver biopsy
Lifestyle modification to treat NAFLD:

- Weight loss through lifestyle modification:
  - 3-5%: reduced hepatic steatosis (1, B)
  - 10%: reduced necro-inflammation (1, B)
    - Improved steatosis, lobular inflammation, ballooning, and NAFLD activity score

- Exercise alone, even without weight loss
  - Can significantly decrease hepatic steatosis (1, B)
  - 2-3 sessions/week, 30-60 minutes, 6-12 weeks

- In children and adults, no evidence to definitively recommend a specific diet or exercise plan
Treatments for pediatric NAFLD/NASH

• **Lifestyle modification** (2, B)

• **Vitamin E**
  
  – **TONIC trial (NASH CRN):**
    
    • RCT of Vitamin E vs. metformin vs. placebo x 96 weeks
    
    • NO difference between groups in sustained ALT reduction
    
    • Vitamin E
      
      – Significantly decreased NASH Activity Score
      
      – Improved NASH resolution (25% Vit E group, 11% placebo)
  
  – **Recommendation**: 800 IU rrr alpha-tocopherol daily for children with **biopsy-proven** NASH or borderline NASH (1, B)
    
    • FDA Recommended daily allowance: 15-30 IU/day
Vitamin E in adults:

- **Vitamin E:** Recommended at 800 IU/day for biopsy-proven, non-diabetic ADULTS as first line therapy (1, B)
  - Improves steatosis, inflammation, ballooning, NASH resolution
  - Does NOT improve fibrosis
  - NASH CRN trials (PIVENS, TONIC) suggest that rrr alpha-tocopherol at 800IU/day helpful
    - 2 previous meta-analyses failed to show histologic benefits
  - Increases all-cause mortality
    - Conflicting data from meta-analyses
    - Recent trial of 400 IU/day associated with increased prostate cancer risk
    - NOT recommended in NASH + DM, NAFLD w/o liver biopsy, NASH cirrhosis, cryptogenic cirrhosis, NAFLD/NASH with other chronic liver disease co-existing (1, B/C)
Other adult medications for NASH:

• **Metformin: Not recommended** (1, A)
  – RCT data for both adults and children
  – No effect on AST/ALT or liver histology
  – No effect regardless of diabetes as co-morbidity

• **Pioglitazone: Recommended in biopsy-proven, non-diabetic ADULTS** (1, B)
  – Meta-analysis (Vernon G et al, 2011):
    • Improves steatosis: OR 4.05, 95% CI 2.58-6.35
    • Improves inflammation: OR 3.53, 95% CI 2.21-5.64
    • Does NOT improve fibrosis: OR 1.40, 95% CI 0.87-2.24
  – Causes weight gain
Other adult medications for NASH:

- **UDCA**: Not recommended (1, B)
  - Several small studies, 1 large RCT: no benefit

- **Omega-3 fatty acids**: Use to treat hypertriglyceridemia in NASH patients, but not specifically to treat NAFLD/NASH (1, B)
  - Large multicenter study ongoing: eicosapentoic acid
  - Other studies small, flawed

- **Statins**: Use to treat dyslipidemia in NAFLD/NASH patients, but NOT as specific treatment for NAFLD/NASH (1, B)
Bariatric surgery and NASH:

- NAFLD/NASH not a contraindication (1, A)
- No RCTs evaluate bariatric surgery as a treatment for NASH
- 2 meta-analyses:
  - Mummadi et al: bariatric surgery improves steatosis, steatohepatitis, fibrosis
  - Cochrane Review: lack of RCT data prevents definitive assessment of bariatric surgery as NASH treatment
- Safety and utility in NASH cirrhosis not established (1, B)
CyNCH trial (NIH-NIDDK-NASH CRN):

- Cysteamine bitartrate delayed-release for treatment of NAFLD in Children
  - Children 8-17 years of age with histologically proven NASH
  - Double-blind, placebo-controlled Phase 2b randomized controlled trial
  - 52 weeks of treatment, 24 weeks post-treatment follow-up
    - 6 follow-up visits
    - Post-treatment liver biopsy
  - 160 children
  - 10 clinical centers (UCSF!)
- Primary outcome:
  - Improved NAS + no worsening of fibrosis
NAFLD Pathogenesis

Two-hit hypothesis

- Chronic ethanol consumption → ↑NADH/NAD⁺ & ↓AMPK, ↑SREBP
- Obesity/Cardiometabolic syndrome
- Insulin resistance
- "1st Hit" → Hepatic Steatosis
- "2nd Hit" → Environmental toxicants, ROS/RNS, cytokines, mitochondrial damage
- ASH/NASH

Lipotoxicity hypothesis

- Serine/threonine kinase (P490) α-oxidation
- Mitochondrial β-oxidation
- VLDL (secreted)
- Lipid droplets (steatosis)
- Lipid toxic intermediates:
  - Phosphatidic acid
  - Lyso phosphatidic acid
  - Lyso phosphatidyl choline
  - Ceramides
  - Diacylglycerols
  - Others
- ROS → Oxidative Stress
- Lipotoxic Liver Injury "NASH"

Mantena SK et al. 2008
Bass NM. Hepatology 2010
Cysteamine bitartrate, delayed

- Cysteine availability = limiting factor in glutathione synthesis
- Glutathione is a major endogenous anti-oxidant
  - Glutathione depletion → hepatocellular injury
    - Acetaminophen liver injury → N-acetylcysteine
    - ?NASH liver injury → cysteamine?
Cysteamine bitartrate, delayed release

- Twice daily dosing
  - ~1/3 the daily dose given to cystinosis patients
- Enteric-coated to decrease GI side effects
- Based on results of phase 2a pilot study
  - 11 children biopsy-proven NAFLD and ALT>60
  - 70% with ALT<40 or >50% reduced from baseline