Case Presentation

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Case

- HPI: 4 yo female with PMHx of obesity sent to ED from clinic with BS of 353. Pt. has had polyuria for the past year, as well as polydipsia. She has a rash that has been present for the past 2 years. She has been gaining weight significantly for the past couple of years.
Case

- PMHx: obesity, rash
- PSHx: none
- All: NKDA
- Meds: Hydrocortisone cream, Clotrimazole cream
- Birth Hx: C-S for LGA
- Social: Lives with mom, dad, 3 siblings. Family is from Tonga.
- Dev: About to start kindergarten.
- Fam: Mom, PGF: T2DM
- Diet: fast food 2-3x wk, soda/juice ½ gallon/day, lots of salty food
• Physical: T35.6 HR 107 RR 20 BP 125/86 Sat 97% RA
  – Weight 56.7 kg (>>95%), Height 118 cm (>95%), BMI 40.7 (>>95%)
  – Gen: Pt. awake, alert, in NAD
  – HEENT: NC/AT, PERRL, MMM, dental caries
  – Neck: no thyromegaly
  – CVS: RRR, no murmurs
  – Lungs: CTA b/l
  – ABD: +BS, obese, NT, ND
  – EXT: full ROM, no edema
  – GU: Tanner 1 female
  – Skin: multiple areas of erythema with excoriations, no active drainage, acanthosis of neck
Case
Case

- Labs:
  - Na 138, K 4.6, Cl 103, CO2 22, BUN 6, Cr 0.5, Glu 209, Ca 9.8, AG 13
  - TB 0.8, TP 8.7, Alb 4.1, AST 325 (15-41), ALT 261 (17-63), AP 524
  - WBC 10.7, Hb 14.4, Hct 41.9, Plt 279
  - Acetone neg, B-OH 0.1
  - Chol 216, TG 318 (35-135), HDL 30, LDL 125
  - Insulin 14.5 (1.9-23), C peptide 4.4 (0.8-3.1)
  - T4 9.8, TSH 2.4
  - HbA1c 12.8 (4.2-5.8)
  - Anti-GAD ab, anti-insulin ab, islet cell ab neg.
Case

• Labs:
  – HAV-IgM neg, HBSag neg, HCV ab neg
  – IgG 2100
  – ANA <1:40
  – Smooth muscle ab 11
  – TTG <3
  – Liver-kidney microsomal ab 5.6
Case

• Liver biopsy:
  – Steatohepatitis with mild activity
  – Mallory body formation and balloon cell change
  – Periportal and central fibrosis
  – Stage 3 fibrosis
  – Stellate cell activity markedly increased indicating rapid progression of scarring process
Obesity

• NHANES 1999-2004
  – 16% of children 2-19 yrs old obese
    • More prevalent in boys, minorities, lower SES
  – Prevalence of BMI >99% - increased from 0.8% in 1976-1980, to 3.8%
  – BMI ≥99% associated with
    • Higher BP, lower HDL, higher insulin, higher LFTs, larger waist circumference

Obesity

Figure 1. Prevalence of body mass index (BMI) ≥99th percentile among US children ages 2 to 19 years, National Health and Nutrition Examination Survey (NHANES) II (1976–1980), NHANES III (1988–1994), and NHANES 1999–2004 by age groupings. \(^*P < .001\) for trends from NHANES II to NHANES III to NHANES 1999–2004. \(^{ab}P < .001\) comparing NHANES II to NHANES 1999–2004. \(^{ab}P < .05\) comparing NHANES III to NHANES 1999–2004. \(^{cd}P \leq .01\) comparing NHANES II to NHANES III. \(^*\)Estimates for NHANES II are based on sample size <50 or relative standard error >30% and may be unreliable.

**Metabolic Syndrome**

- Pediatric metabolic syndrome
  - Increased waist circumference plus
  - 2 of the following:
    - Elevated triglycerides
    - Elevated BP
    - Low HDL
    - Abnormal glucose tolerance
  - In adults, risk factor for T2DM, cardiovascular disease, and all causes of mortality

T2DM

• NHANES 3
  – Diabetes prevalence 0.4% of 12-19 yo
    • 31% T2DM

• T2DM
  – F>M, majority overweight/obese at presentation
  – Present often during puberty
  – Strong family history

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Acute—symptomatic</td>
<td>Slow—often asymptomatic</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>Weight loss</td>
<td>Obese</td>
</tr>
<tr>
<td></td>
<td>Polyuria</td>
<td>Strong family history of Type 2 diabetes</td>
</tr>
<tr>
<td></td>
<td>Polydipsia</td>
<td>Ethnicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acanthosis nigricans</td>
</tr>
<tr>
<td></td>
<td></td>
<td>polycystic ovarian syndrome</td>
</tr>
<tr>
<td><strong>Ketosis</strong></td>
<td>Almost always</td>
<td>Usually absent</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td>c-Peptide negative</td>
<td>c-Peptide positive</td>
</tr>
<tr>
<td></td>
<td>ICA positive</td>
<td>ICA negative</td>
</tr>
<tr>
<td></td>
<td>Anti-GAD positive</td>
<td>Anti-GAD negative</td>
</tr>
<tr>
<td></td>
<td>ICA 512 positive</td>
<td>ICA 512 negative</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Insulin</td>
<td>Oral hypoglycaemic agents initially</td>
</tr>
<tr>
<td><strong>Associated autoimmune disorders</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
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NAFLD

• NAFLD
  – Accumulation of macrovesicular fat in hepatocytes, without consumption of excessive alcohol
  – Prevalence in children 2.6-9.6%, increases to 12-80% of overweight/obese children

• NASH
  – Fatty liver disease causing liver inflammation and varying degrees of hepatic fibrosis
    • Inflammation and fibrosis of portal area
  – Can progress to cirrhosis and hepatocelluar carcinoma

NASH

Pathogenesis – 2 hit hypothesis
- 1\textsuperscript{st} step: fat accumulation in the liver
- 2\textsuperscript{nd} step: oxidative stress, lipotoxicity, adipocytokines, alterations in mitochondrial permeability & stellate cell activation cause liver injury \(\rightarrow\) NASH


NASH

- IR – results from inability of adipose tissue to expand & accommodate excess fats
- Abnormally suppressed lipolysis
- Increased gluconeogenesis & de novo lipogenesis
- Maladaptive organization of adipose tissue in response to excess nutrients results in inflammatory signals to cause progression to NASH

NAFLD

• Clinical Presentation
  – Insidious
  – Fatigue, malaise, vague RUQ discomfort
  – Hepatomegaly
  – Acanthosis nigricans
  – Hypothyroidism, OSA
  – Normal to elevated aminotransferases

NAFLD

Diagnosis

Diagnosis

Candidate criteria for immediate liver biopsy in suspected pediatric NAFLD (if liver biopsy of all such patients is not routine)

- Young age (<10-years-old)
- Hepatosplenomegaly
- Very elevated serum AST or ALT
- Very severe insulin resistance (by HOMA-IR)
- Detectable nonspecific autoantibodies
- Inconclusive results from biochemical tests relating to Wilson disease
- Co-morbid liver diseases such as chronic viral hepatitis
  - or α₁-antitrypsin deficiency
- Hypothalamic disorder
- Family history of severe NAFLD
- Planned pharmacological intervention

Diagnosis

• Biomarkers
  – Inflammation
    • IL-6, TNF-α
  – Oxidative stress
    • Ox-LDL, TBARS
  – Apoptosis
    • CK-18
  – Fibrosis
    • ELF score – HA, PIIINP, TIMP-1

Diagnosis

- NAFLD scoring system
  - Steatosis (0-3)
  - Lobular inflammation (0-2)
  - Hepatocellular ballooning (0-2)
  - Fibrosis (0-4)
  - Microvesicular steatosis
  - Acidophil bodies
  - Microgranulomas
  - Lipogranulomas
  - Portal inflammation
  - Pigmented macrophages
  - Megamitochondria
  - Mallory hyaline
  - Glycogenated nuclei

Diagnosis

Adult NASH – steatosis, ballooning degeneration, intralobular inflammation, perisinusoidal fibrosis

Pediatric NASH – macrovesicular steatosis, portal inflammation, expansion of portal tract due to fibrosis

## Diagnosis

<table>
<thead>
<tr>
<th>Quality</th>
<th>“Pediatric-type” NASH</th>
<th>“Adult-type” NASH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency in children</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Steatosis</td>
<td>More pronounced</td>
<td>Less pronounced</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Portal</td>
<td>Lobular</td>
</tr>
<tr>
<td>Ballooning</td>
<td>Not present</td>
<td>Usually present</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>Portal or none</td>
<td>Perisinusoidal/pericentral</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Can occur</td>
<td>Can occur</td>
</tr>
</tbody>
</table>

Based on retrospective analysis of 100 children described by Schwimmer et al [23].

• A,B: absent ballooning degeneration & peri-sinusoidal fibrosis with steatosis & portal inflammation
• C: portal fibrotic expansion & steatosis
• D: peri-portal inflammation w/o steatosis around portal tract & mild fibrosis around central vein

15 yo with cirrhosis due to NASH
- Fat fraction map
- double-contrast enhanced MR showing fibrotic reticulations mostly in liver periphery

Treatment

• Diet
  – Low-fat, low-glycemic index foods
  – Hypocaloric diet 25-30 cal/kg/d if overweight

• Exercise

• Metformin

• Vitamin E

• Ursodeoxycholic acid

NASH & Sucrose

• Methionine & choline deficient diets
  – Cause hepatic steatosis & inflammation
    • Enhanced FA uptake by liver
    • Impaired secretion of hepatic TG
  – Commercial formulas enriched in sucrose & fat
• MCD-sucrose and MCD-starch – identical diet-related abnormalities in hepatic FA uptake & TG secretion

NASH & Sucrose

- MCD-sucrose – hepatic steatosis, hepatocellular apoptosis, ALT elevation, lipid peroxidation, hepatic inflammation

Hepatic DNL and TG synthesis 2x higher in MCD-sucrose than in MCD-starch.

Sucrose critical for pathogenesis of MCD-mediated steatohepatitis. Saturated FA, which are products of DNL, are mediators of hepatic toxicity in this model.

NASH & Sucrose

- Rats fed chow or HF/HS diet
  - No biochemical or histological evidence of injury
- Sedentary rats fed HF/HS – higher insulin, hepatic steatosis, Kupffer cell content, cytokine expression

NASH & Sucrose

Summary

• The prevalence of obesity is increasing in all pediatric age groups
• T2DM is being diagnosed more often in kids
• NAFLD is more common in obese children and can progress to NASH due to high fat diet and insulin resistance
• NAFLD is usually asymptomatic
Summary

- NAFLD/NASH can be diagnosed by labs (increased AST, ALT, insulin, and TG), fat fraction MRI, and liver biopsy
- Typical histology in peds shows steatosis, portal inflammation, and portal fibrosis
- Treatment of NASH includes diet, exercise, metformin, and vitamin E
- Animal models show that sucrose and a sedentary lifestyle contribute to NASH