Ask the Experts: Pediatric Liver Disease

Fatty Liver Disease in Children

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What is NAFLD?

Presence of excess fat in liver demonstrated by imaging or biopsy in the absence of alcohol intake and viral, metabolic, autoimmune and drug induced liver disease.

Simple steatosis $\rightarrow$ NASH $\rightarrow$ Advanced Fibrosis

- Prediabetes
- Type 2 Diabetes
- Diabetes Complications
What is the Impact of NAFLD?

Pediatric NAFLD:
Overall: ~ 10%
15-19 years: ~ 17%
Obese: ~ 50%
~ 5 million children

NAFLD – Rising Epidemic

Trends in the prevalence of suspected NAFLD among US adolescents (12-19 years)

Prevalence of NASH and Advanced Fibrosis

- Prevalence of suspected advanced fibrosis remains low at 0.2% of US adolescents.
- Burden of NAFLD is highest among Mexican-American adolescents with approximately NASH in 5% and advanced fibrosis in 1.4% during 2005-2010.

Selvakumar et al. HEPATOLOGY, VOLUME 64, NUMBER 1 (SUPPL) 2016
Liver Transplantation for Pediatric NAFLD

14 patients under 18 years of age and 20 patients between 18 and 25 years of age received LT for NASH cirrhosis

Alkhouri et al. Transpl Int. 2016
What Causes NAFLD?

Nobili et al. Journal of Hepatology 2013

Ask the Experts: Pediatric Liver Disease
NAFLD – Clinical Presentation

- Mostly no symptoms

- Diagnosed based on elevation of liver enzymes or evidence of fat in liver on ultrasound

- Mean age of diagnosis: 11-13 years

- Nonspecific right upper quadrant abdominal pain from stretching of liver capsule and fatigue
How do we find NAFLD?

• Screening recommended between ages 9 and 11 years for all obese children (BMI ≥ 95th percentile) and for overweight children (BMI ≥ 85th and < 94th percentile) with additional risk factors (central adiposity, insulin resistance, prediabetes or diabetes, dyslipidemia, sleep apnea, or family history of NAFLD/NASH).

• Screening methods: Liver enzymes and/or Ultrasound of liver
Staging of Liver Fibrosis – Does it Matter?

Presence of liver fibrosis is the most important predictor of overall and liver related mortality

Angulo et al Gastroenterology 2015
Ask the Experts: Pediatric Liver Disease
Noninvasive – Tissue Elastography
Pediatric NAFLD Management

- **Lifestyle interventions:** Diet, physical activity, weight loss
- **Pharmacologic:** Metformin, Vitamin E
Hypocaloric diet, increasing physical activity, and gradual weight loss remain the mainstay of therapy in pediatric NAFLD.
Aerobic or Resistance Training?

Moderate/ Vigorous Exercise: 30-45 min/day
How do we manage NAFLD in children?

Evaluation:

• Evaluate for other causes of elevated ALT and hepatic steatosis (viral hepatitis, Wilson disease, autoimmune hepatitis)
• Screen for extrahepatic comorbidities such as DM, hypertension, dyslipidemia and obstructive sleep apnea
• Assess the severity of disease with tissue elastography
• Liver biopsy in children with advanced fibrosis (F ≥ 3)

Treatment:

1. Diet (Low carbohydrate diet, partial liquid diet)
2. Exercise (community based programs, comprehensive weight loss program)
3. Vitamin E 400 IU BID in children with NASH (elevated ALT, biopsy-proven, evidence of fibrosis on Fibroscan)
4. Metformin 500 mg BID in children with evidence of insulin resistance or prediabetes or DM
Biliary Atresia

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The MetroHealth System
Assistant Professor of Pediatrics
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Biliary Atresia
What is Biliary Atresia (BA)

• A liver disease characterized by a fibro-obliterative process of the bile ducts causing blockage to bile flow.
• Bile is a substance produced by the liver, and transported via bile ducts to the intestine, where it performs digestive and excretory functions.
• Obstruction of bile flow leads to build-up of toxic substances in the blood and damage to the liver (cholestatic disease).
Types of Biliary Atresia

• 70-85% - Perinatal BA (isolated BA)
• 10-15% - Embryonal BA (laterality defects) - other birth defects like intestinal malrotation, situs inversus, polysplenia, asplenia (BASM), etc.
• 5-10% - other congenital malformations - intestinal, kidney, heart, etc.
Biliary Atresia

• How common is BA?
• It’s rare; 1:8000-1:18,000 live births
• Who is affected?
• Infants
• Slightly more common in female infants
• African American and Asian babies are more affected
• What causes BA?
• Not well understood. Theories: viral infections, other environmental triggers (toxins), genetic causes (e.g. CFC 1 gene and abnormal embryonic development), immunologic injury, etc.
How may BA present?

- Most babies full term and born healthy!
- Persistent Jaundice (yellow coloration of eyes and skin) (>15 days)
- New onset jaundice in the first few weeks of life (2-6 weeks)
- Pale stools (Acholic stools)
- Dark colored urine
- Poor weight gain
- Abdominal distension (liver, spleen enlargement)
- May have other symptoms if other birth defects are present (embryonal BA)
Signs and Symptoms of BA in infants

Infant Stool Color Card

Abnormal
It is essential to observe your baby’s stool color continuously after discharge from a nursery. If the stool color resembles the numbers 1–3 (white, clay-colored, or light yellowish), the possibility on your baby suffering from biliary atresia is higher. Please take this card and your baby to consult a doctor as quickly as possible. Regardless of what the stool color is, please bring this card to your doctor at 36 days of age for health check. If the baby cannot go back for health check, please fill in the number of the color resembling your baby’s stool, along with the following blanks, and mail this card to our registry center.

Normal
The baby’s stool color is most like No.____
Date of this kind of stool

Name of the baby  Birthday
Name of the mother  Tel.
Address
The hospital or clinic where the baby was born

If the number is No.1–3, please inform us by fax immediately. We will provide the related information and help you out.

Fax: 02-2388-1798; Tel: 02-2382-0884

Infant Stool Color Card Registry Center
Jaundice and abdominal distention
Making the diagnosis: Multi-step process

- Initially a series of blood tests to classify type of jaundice
- **Direct hyperbilirubinemia, increased AST/ALT, increased GGT**
- Ultrasound of liver and hepatobiliary tract
- Findings:
  - Normal (20%),
  - Absent gall bladder (0-53%) or other GB dysmorphologies
  - **Triangular cord sign (sensitivity 85%, specificity 97%)**
Making the diagnosis: Multi-step process

- **HIDA Scan**
- Scintigraphy-based test which evaluates for the excretion of a radiotracer dye from the liver via bile ducts into the intestine
- Role in diagnosis is controversial; screening for BA
- It is helpful if the study shows excretion of tracer into the bowel, not necessarily helpful, if it doesn’t show excretion into the bowel.
- Sensitivity 98.7% (98.1-99.2%) and specificity 70.4% (range 68.5-72.2%)

HIDA Scan

Figure 2: The baby underwent Kasai procedure at AIIMS (Pediatric surgery department) and 1 week after surgery HIDA scan showed excellent hepatic uptake of radiotracer and prompt intestinal excretion of bile (within 30 min) and no hepatic retention. This is successful Kasai operation.
Making the diagnosis: Multi-step process

- Liver Biopsy
- Characteristic findings of bile duct obstruction
- Intraoperative Cholangiogram (Definitive Diagnosis)
- Injection of the bile ducts with contrast in the operating room to check for drainage into intestines
Liver Biopsy
Management

• Kasai Portoenterostomy (KPE) is performed promptly upon diagnosis
• Goal: Restore bile flow from liver to small intestine
Kasai outcomes

- Felt to be best if KPE done within first 60 days in experienced centers
- Disappearance of jaundice is best correlated with reaching native liver survival (NLS) at 2 years after KPE
- After Kasai, About 55% survival with native liver (NLS) at 2 years
- Between 20—30% survival with native liver (NLS) at 20 years
- Other children- primary failure of Kasai, complications from Kasai, progressive failure and portal hypertension (liver disease progresses) will need a liver transplant as a definitive Rx.

Other medical management

- Fat soluble vitamin deficiencies
- Fat malabsorption and malnutrition Rx
- Complications of progressive liver disease (portal hypertension, ascites, coagulopathy, etc.)

- Curative Rx: Pediatric Liver transplant.
Thank you and Questions
Liver disease in Teenagers

Vera Hupertz, MD
Medical Director Pediatric Liver Transplant
Transplant Hepatology

Cleveland Clinic Children’s
Ask the Experts: Pediatric Liver Disease

Agenda

- Symptoms of liver disease
- Autoimmune hepatitis
- Sclerosing Cholangitis
- Hepatitis C
Symptoms of liver disease

- Might not be any!
- Fatigue (but what teenager is not!)
- Jaundice of the skin and eyes
- Itching
- Bruising/bleeding
- Weight loss or poor growth
AUTOIMMUNE DISEASES

Brain
- Multiple Sclerosis
- Guillain-Barre Syndrome
- Autism

Blood
- Leukemia
- Lupus Erythematosus
- Hemolytic Dysglycemia

GI Tract
- Celiac’s Disease
- Crohn’s Disease
- Ulcerative Colitis
- Diabetes Type 1

Nerves
- Peripheral Neuropathy
- Diabetic Neuropathy

Lung
- Fibromyalgia
- Wegener’s Granulomatosis

Thyroid
- Thyroiditis
- Hashimoto’s Disease
- Graves’ Disease

Bones
- Rheumatoid Arthritis
- Ankylosing Spondylitis
- Polymyalgia Rheumatica

Muscles
- Rheumatoid Arthritis
- Ankylosing Spondylitis
- Polymyalgia Rheumatica

Skin
- Psoriasis
- Vitiligo
- Eczema
- Scleroderma

Over 100 Different Types of Autoimmune Disorders
Why do people get autoimmune disease?
Diagnosis of Autoimmune Hepatitis

• Laboratory tests
  – Liver enzymes are elevated (AST and ALT)
  – Autoimmune markers
    • ANA
    • Smooth muscle antibodies
    • Elevated antibodies in the blood (IgG)
    • LKM
  – Liver biopsy

Determine Type 1 or 2
Treatment

• Medications to calm down the immune system
  – Steroids like prednisone
  – Immunomodulators
  – Anti-rejection medications
Sclerosing cholangitis

• Disease of the bile ducts
  – Can be “idiopathic”
  – Can be due to infections
  – Eosinophilic
  – Autoimmune
  – Chemotherapy induced

• Can be associated with other diseases or can occur by itself
  – Histiocytosis X
  – Immune deficiency states
  – Inflammatory bowel disease
Anatomy of the liver

Sclerosing Cholangitis

Bile is produced by the liver & stored in the gallbladder

Inflammation & Scarring of the Bile Ducts
Diagnosis

• MRI – MRCP (magnetic resonance cholangiopancreatogram)
• ERCP – endoscopic retrograde cholangiopancreatogram
• Liver biopsies – done to evaluate for other disease in the liver
Treatment

• Mostly at symptoms
• Urso
• Treat the underlying disease if present
Liver transplantation

• Option for both Autoimmune hepatitis and PSC if they progress
• Some risk of it coming back in the new liver
Hepatitis C

• Infection spread by exposure to blood
• Currently on the rise in teens / young adults due to IV drug use
• Symptoms
  – JUST LIKE ALL THE OTHERS
• Treatment
  – May not be needed if they clear on their own
  – New drugs to kill the virus
    • Cure rates of almost 99%
    • Each case evaluated with regards
      – Length of time of disease
      – Amount of scarring in the liver
      – Other associated illnesses
Summary

• Most teenagers with liver disease don’t have symptoms
• Symptoms, when present, are vague except if they have jaundice
• Important to evaluate and have testing done in centers with experience and teams to support
Thank you
Case 1

• 13 y.o. girl is brought to your office for evaluation of abdominal pain that has been present for over 4 months. Her pain is poorly localized to the periumbilical area without localization or radiation. She rates her pain as a 6/10. Her pain is worse in the morning and also may be present in the afternoon and before bed. There are no specific triggers such as diet or activity that precipitate her pain. She does not have a history of change in her appetite, nausea, or vomiting, change in her stool pattern or weight loss. Otherwise healthy.

• Parents concerned because of missing school 1-2 days a week for the last few months.

• Physical examination is normal.

• Laboratory workup was negative
Chronic abdominal pain

• Three groups
  – Organic diseases: pain associated with specific GI problems such as Crohn’s disease, peptic ulcer, pancreatitis, etc.
  – Abdominal pain with identifiable pattern to the symptoms such as IBS, non-ulcer dyspepsia, etc.
  – No organic disease and no identifiable pattern
Types of Abdominal Pain

• Acute:
• Chronic or Recurrent abdominal pain
  – Functional abdominal pain
Chronic Abdominal Pain in Children

• One of the most common complaints in children and adolescents
  – 13% of middle school children
  – 17% of high school children
  – Affects activity in 20%

• Functional vs organic
  – 80-90% functional
Chronic abdominal pain

• ≥3 episodes of abdominal pain
• pain sufficiently severe to affect activities
• episodes occur over a period of ≥3 months
• no known organic cause
Initial visit

- Comprehensive history and exam
  - Reassurance to the family and patient
  - Your taking this as a serious issue
  - Diary: time of day, location and severity, triggers, duration, interventions

- Ask what has been tried in the past
  - Duration of treatments
  - Effects

- Ask what they think is going on or what they are afraid of
  - Address the concerns directly
History

- Pain description
  - Time, location, duration, severity (FACES scale 1-5), triggers, alleviators, position of the body during pain
- Bowel and bladder symptoms
- Menses and relationship to the pain.
- Psychosocial history
- Red flags
## Pain Diary

- Time of day the pain occurred
- Pain location and severity using a scale of zero (no pain) to five (worst pain) or the FACES scale and including whether the pain prevented activities
- Pain duration
- Possible triggering factors: foods, activities, stressors, thoughts, feelings
- Remedies/interventions

<table>
<thead>
<tr>
<th>Time</th>
<th>Pain location</th>
<th>Pain Severity</th>
<th>Duration</th>
<th>Activity and whether it needed to be stopped</th>
<th>Possible trigger</th>
<th>Intervention</th>
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HEADSS

- Home
- Education
- Activities
- Drugs
- Sexuality
- Suicide
Physical Exam

- General appearance
- Growth parameters
- Vital signs
- Abdominal exam
  - Palpation
  - Guarding
  - Carnett sign for abdominal wall pain
- Psoas sign
- Sexual maturity
- Perianal and digital exam
- Pelvic
Red Flags in Chronic Abdominal Pain

History

- Persistent RUQ or RLQ pain
- Dysphagia
- Persistent vomiting
- GI blood loss
- Nocturnal diarrhea
- Nocturnal pain
- Arthritis
- Unexplained fever
- Family Hx IBD or celiac

Physical exam

- Involuntary weight loss
- Deceleration in linear growth
- Oral aphthous ulcers
- Localized tenderness
- Hepatomegaly or splenomegaly
- Perianal disease
- Delayed puberty
- Guaiac positive stools
Lab tests

- As needed if there are any red flags
- Stool testing
  - Rectal bleeding or occult blood
  - Calprotectin
  - Ova & Parasites
- Avoid food allergy testing unless specific symptoms
- Children with red flags
  - CBC
  - WSR and/or CRP
  - Complete metabolic panel
  - Urinalysis
  - Celiac testing
  - Thyroid testing in chronic constipation
Other tests in Children with Red Flags

• Imaging
  – Ultrasound (abdominal and/or pelvic)
  – KUB
  – UGI if vomiting to r/o malrotation, adhesions, etc
  – CT or MR: plain or enterography

• Endoscopy
Organic versus Functional

- **Organic disorders**
  - Structural, physiologic or biochemical abnormalities
  - Often have Red Flags

- **Functional disorders**
  - Combination of symptoms without identifiable or suspicion for an organic problem (no red flags, normal PE, negative stool for blood)
  - Poorly localized, ill defined, periumbilical
  - Relatively short duration, stress triggers
  - Can have autonomic features
  - Anxiety or depressive symptoms may be present
  - Positive family history of GI complaints (IBS, reflux, constipation).
  - Limited testing, make a positive diagnosis and educate)
Functional abdominal pain

• Two age peaks
  – 5-7 yrs. age, boys=girls, 5-8% children
  – 8-12 yrs. age, girls>boys, 25% children
Functional Abdominal Pain

• Diagnosis/counseling:
  • Positive diagnosis based on symptoms and absence of organic symptoms
  • Reassurance and return to normalcy
  • Consider psychologic evaluation and therapy if pain persists

• Possible mechanisms
  • Visceral hyperalgesia
  • reduced threshold for pain
  • abnormal pain referral after rectal distension
  • impaired gastric relaxation response to meals
Irritable bowel syndrome (IBS)

• Rome criteria:
  – Continuous or recurrent symptoms of abdominal pain or discomfort relieved with defecation, and/or associated with a change in frequency of stool, and/or associated with a change in consistency of stool
  – No red flags
  – Not a diagnosis of exclusion
  – Frequently associated with long term history of constipation or preceding gastroenteritis
  – Often a family history
Impact of IBS

• 10-25% seek medical care
• Economic impact: $25 billion annually
• Reduced quality of life
• Absenteeism from work 3x normal
Diagnosis of IBS

- Suggestive history, normal physical exam, normal growth history
- Watch out for “Red flags”
- Limited screen for organic disease
  - CBC, ESR, Stool studies for bacteria and parasites, celiac screen, lactose breath hydrogen testing
- Evaluate for possible dietary triggers/effects
- Inquire into psychosocial history
Treatment for IBS

• Reassurance that though pain, not serious or life threatening

• Diarrhea predominant: avoid sorbitol, fructose, lactose (if positive test), gas-forming legumes

• Constipation: fiber (age +5 g), osmotic laxative, or softener/lubricant
Low-FODMAP Diet

• Fermentable oligosaccharide, monosaccharide, polyol diet
• Variable results (30-75% improved)
• Drawbacks:
  – Cognitively able patients/parents
  – Children need guidance, and difficulty at social or school functions
  – Reduces healthy high-fiber food
<table>
<thead>
<tr>
<th>Food category</th>
<th>High-FODMAP</th>
<th>Low-FODMAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetables</td>
<td>Artichokes, asparagus, beetroot, celery, garlic, leek bulb, legumes, onion and garlic salts, onions, Savoy cabbage, sugar snap peas, sweet corn</td>
<td>Alfalfa, bean sprouts, bok choy, choy sum, bell peppers, carrot, chives, cucumber, fresh herbs, green beans, lettuce, tomato, zucchini</td>
</tr>
<tr>
<td>Fruits</td>
<td>Apple, mango, pear, nectarine, peach, nashi pear, plum, watermelon</td>
<td>Banana, orange, mandarin, grapes, melon</td>
</tr>
<tr>
<td>Milk and dairy</td>
<td>Cow’s milk, cream, custard, ice cream, soft cheese, yogurt</td>
<td>Hard cheese, lactose-free milk, lactose-free yogurt</td>
</tr>
<tr>
<td>Protein</td>
<td>Legumes/pulses</td>
<td>Chicken, fish, meats, tempeh, tofu</td>
</tr>
<tr>
<td>Breads and cereal</td>
<td>Rye, wheat pasta, wheat-based cereals with dried fruits, wheat containing bread</td>
<td>Gluten-free bread and sourdough spelt bread, rice bubbles, gluten-free pasta, oats, quinoa, rice</td>
</tr>
<tr>
<td>Cookies and snacks</td>
<td>Rye crackers, wheat-based biscuits</td>
<td>Corn thins, gluten-free biscuits, rice cakes</td>
</tr>
<tr>
<td>Nuts and seeds</td>
<td>Cashews, pistachios</td>
<td>Almonds (&lt;10 nuts), pumpkin seeds</td>
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</tbody>
</table>
IBS associated with constipation

• Often starts as incomplete evacuation, so therapy is aimed at improving bowel function
  – Initial cleanout
  – start with softeners (polyethylene glycol, lactulose, mineral oil)
  – motivators to go
    • sticker charts, milk of magnesia, senna, enema
  – stool diary to establish a routine
  – lasts anywhere from 2 - 6 months

• Goal: 1-2 BMs per day for 2-3 months
Therapy for IBS

• Non-pharmacologic treatment \(^{(2)}\)
  – Probiotics (lactobacillus rhamnosus GG or VSL#3) – probable benefit
  – Guar gum but not other fiber - inconclusive
  – Hypnotherapy and cognitive behavioral therapy – probable benefit
  – Functional disability improved by yoga
  – Peppermint oil \(^{(1)}\)
    • pediatric study of 50 patients with IBS \((Kline 2001)\)
    • Most adult studies show conflicting data

Drug therapy for IBS

- "Antispasmodics": dicyclomine, hyoscine, mebeverine, and octylonium
- Tricyclic antidepressants: imipramine or amitriptyline
  - anecdotal reports of use in childhood abdominal pain
  - offers both central analgesia and anticholinergic effects (neuromuscular)
  - imipramine better in children with constipation
  - amitriptyline better if there is sleep disturbance
Future agents for IBS

• Diarrhea
  – 5-HT\textsubscript{3} antagonists: retard small bowel and colonic transit (alosetron)
  – Selective M3 type anticholinergics: anti-spasmodic and antidiarrheal potential
  – CCK antagonist: loxiglumide

• Constipation
  – 5-HT\textsubscript{4} agonists: accelerates transit (SB + colon)
    • Tegaserod and prucalopride
Dyspepsia

• Persistent upper abdominal pain or discomfort
• May arise from disease (*H. pylori*, Crohn’s, GERD, antral gastritis, PUD) or be functional
• Two types:
  – Ulcer-like pain
  – Dysmotility-like dyspepsia
Dyspepsia types

• Ulcer-like
  – upper abdominal pain
  – often relieved by food or anti-acid therapy
  – possible night time awakening

• Dysmotility-like
  – pain is not predominant
  – primary symptoms of nausea, bloating, early satiety, postprandial fullness, retching or vomiting, or bloating
Pathophysiology of dyspepsia

• Disordered gastric electrical rhythm
• Delayed gastric emptying
• Abnormal gastroduodenal motility
Evaluation of dyspepsia

• Identify treatable issues
  – Detailed history, PE, growth parameters
  – Symptoms of heartburn and regurgitation - GER
  – Sign/Symptoms of organic disease: radiation of pain, weight loss, fever, diarrhea, vomiting, blood in stool or emesis
  – Exposure history for *H. pylori*: poverty, crowding, children of Third World country parents, + family hx *H. pylori*, preceding viral illness
Treatment of dyspepsia

- Dietary changes to avoid aggravating foods
- Avoid medications that may aggravate
- Early satiety: smaller, frequent, low fat meals
- Trial of H₂-histamine receptor antagonist
- Recurrence of pain or lack of response may warrant further testing
  - upper endoscopy, lab work, ultrasound
Treatment of dyspepsia

• Prolonged H2 receptor antagonists
  – Proton pump inhibitors, if symptoms are persistent
• Low dose tricyclic antidepressants
• Metoclopramide may reduce nausea
H. pylori in chronic abdominal pain

- 73 children (29 positive H. pylori histology)
  - 83% of positive patients were non-Swiss
- All patients with H. pylori had abnormal histology
- With therapy, 79% had either complete resolution of symptoms or improvement
- 40% of histologic negative patients had positive serologies

Ask the Experts: Pediatric Liver Disease
H. pylori epidemiology

- Developed countries - 50% 60 year olds
- Developing countries - 50-60% infected by school age
- Person to person passage (73% of parents of infected children have positive antibody response, 80% siblings
- Clustering within institutions for the mentally handicapped
Abdominal migraines

• Definition: paroxysmal recurrent abdominal pain with nausea and/or vomiting, a hx of wellness between episodes, no other identifiable causes, positive family hx of migraines among 1st degree relatives
  – may be associated with pallor, headache, photophobia, aura
  – may have abnormal visual evoked response
Treatment of abdominal migraines
(Worawatianakul et al)

- Treatment reviewed: propranolol (n=24) Vs. cyproheptadine (n=12)
  - 75% vs. 33% had a good response with propranolol (NS)
  - 50% vs. 8% had a fair response with cyproheptadine (NS)
  - 17% didn’t respond in either group
  - Flawed because not randomly assigned, no placebo

- Propranolol
- Pizotifin also used with some success
- Anti-depressant

Israil et al. Mymensingh Med J.
2013; 22:93-100
Cannabinoid Induced Hyperemesis

• Confused with cyclic vomiting
  – Same reliever: hot showers

• May be associated with acute ingestions, chronic, or acute on chronic

• Severe vomiting, abdominal pain.

• Young children may have coma with apnea or preparatory depression, seizures.
  – Repeated exposures: behavioral changes, lethargy, intoxication symptoms
Appendiceal colic

- Stevenson: Symptoms limited to pain in the RLQ, colicky, may be exacerbated by eating, some autonomic symptoms, tenderness at McBurney’s point
  - 76% girls, mean age 12.3 yrs., duration of pain 1-8 years
  - Testing: CBC and U/A not helpful
  - Histology: fibrosis or fecaloma in 56%, 14% normal histology
- Outcome: If specific criteria met, 49 of 50 without pain at 1 year.
  - 1/50 had subsequent development of renal stones that may have been the cause of original pain
  - Radiographic studies were not helpful

Appendectomy findings

- Rate of negative appendectomies on the decline
  - Positive appendectomy: appendicitis, fecoliths, worms, endometriosis, or tumor
  - 76% positive appendectomies; 71.3% acute appendicitis
  - Fecoliths and worms were a known cause of appendiceal colic mostly with normal appendices

Organic causes of chronic abdominal pain

• Gastrointestinal
  – constipation
  – peptic ulcer disease
  – *H. pylori* gastritis
  – IBD
  – gallstones
  – recurrent volvulus
  – food intolerance
  – cystic fibrosis
  – Celiac disease

• Infections and/or inflammatory
  – UTI
  – appendiceal colic
  – parasitic infections
  – HSP
  – pancreatitis
  – TB
  – discitis
  – Crohn’s disease
Organic causes of abdominal pain

• Neurologic
  – abdominal migraines
  – abdominal epilepsy
• Metabolic
  – porphyria
  – hyperparathyroidism
  – diabetes
• Hematologic
  – sickle cell disease
• Other
  – UPJ obstruction
  – drugs (NSAIDS)
  – lead
  – abuse
  – foreign body
  – post surgical
  – gynecological problems
  – slipping rib syndrome
Approach to Metabolic Disorders

Kadakkal Radhakrishnan, MD
MRCP(UK), MRCPCH, FAAP
Pediatric Hepatologist & Gastroenterologist
Cleveland Clinic Children’s
What are metabolic disorders?

- Include a group of medical conditions that involves abnormalities in
  - Processing of carbohydrates,
  - Protein
  - Fats
  - other chemicals in the body
- Or could also grouped into types based on the organelles (small components of the cell) involved,
  - lysosomal storage disorders.
  - Peroxisomes
Cell organelles
Metabolic disorders

• Are very uncommon
• Need a high index of suspicion to diagnose
• Metabolic disorders occasionally may have special diagnostic features
• Often require special testing to prove the diagnosis
• Can go into crisis triggered by specific events
What are some signs of metabolic disorders

- Low glucose
- Increased acid
- Seizures
- Developmental delay
- Change in mental status
- Jaundice and liver failure
- Exercise induced cramping
- Abnormal pigmentation
- Abnormal odor
- Skin rash
- Low white cell count and platelets
- Organomegaly
Odors- rare these days

- Mousy- PKU
- Maple syrup- branched chain amino acid dehydrogenase
- Sweaty feet- isovaleric acidemia
- Cabbage- tyrosinemia
What triggers metabolic disorders?

- Prolonged fasting
- Infections that prevent eating appropriately
- Eating specific foods
- Certain medications
- Over exertion/prolonged exercise
What happens with fasting

• Break down of glycogen – mostly stored in the liver
  – Lasts 8-12 hours irrespective of age
• Break down fat
  – To form ketones
  – Ketones form important fuel for the heart and brain
• Make new glucose- gluconeogenesis
If hypoglycemic- low sugar!

- When sugar is < 60, it is considered hypoglycemia
- Child becomes irritable
- Jittery or shaky
- Or becomes unresponsive
- And sometimes develops seizures
If hypoglycemic- low sugar!

- Check urine ketones- low in
  - Fatty acid oxidation disorders
- Blood gas
  - Normal generally in fatty acid oxidation disorders
  - Abnormal in organic acidemias
What other investigation?

• Blood count
  – Neutropenia and thrombocytopenia
• Electrolytes and Bicarbonate (CO2)
• LFTs- abnormal in fatty acid oxidation and organic acidemias, relatively normal in tyrosinemia
• Ammonia (NH3)- elevated in urea cycle disorders, organic acidemia and fatty acid disorders
More testing!!

- Serum amino acids- fasting preferred
- Urine organic (+/- amino acids)
- Blood for genetic testing
- Fibroblast culture (from skin), or liver or muscle biopsy for specific enzyme assay and functional studies or genetic studies.
Long term treatment

• Special diet
• Maintain adequate growth and development
• Adequate protein
• Teaching- parents about the disorder, diet and complications
• Treatment of complications- acidosis, long-term liver disease and follow ups.
Treatment for acute events

• Maintain glucose levels and prevent catabolism
  – Often requires using 10% dextrose and starting special diet when ready
• Treat any precipitating cause
• Treat elevated NH3
  – Medications to reduce NH3 vs dialysis
• Maintain acid base balance
• Scavengers of abnormal metabolites-
  – IV or oral carnitine +/- glycine
Types of metabolic disorders

- Carbohydrates metabolism
- Fatty acid oxidation disorder
- Amino acid disorders
- Purine and pyrimidine disorders
- Disorders of haem synthesis
- Glycosylation disorders
- Storage disorders
- Disorders of bile acid synthesis
- Disorders of energy metabolism
Some specific Disorders - Glycogen Storage Disorders (GSD)

• Glycogen is the form of starch that is
  – stored in the liver and muscle and
  – forms a source of glucose and therefore energy in between meals and when fasting

• Most of the glycogen storage disorders
  – affect the breakdown of glycogen and
  – leads to accumulation of glycogen in the liver and muscle
GSD 1

• GSD 1 is the most severe form
• Patients are prone for severe drop in glucose (hypoglycemia) after a few hours of fasting.
• They require frequent feeds/meals to avoid low glucoses
• After the first year of life, frequent intake of uncooked corn starch is required to help maintain glucoses and prevent complications.
Other GSDs- ketotic types

- Namely GSD III, VI, IX and 0
- Management involves dietary modifications with uncooked corn starch and extra proteins.
- All these patients can go on to lead normal lives with close monitoring and support.
Mitochondrial disorders

• Mitochondria are the power house of the cell and is involved in generating energy molecules required for the bodily functions.
• These patients may have varying range of health concerns
  – Developmental delay & seizures
  – Gastrointestinal manifestations including feeding problems, gastroesophageal reflux, constipation and motility problems
  – Liver dysfunctions
• Diagnosis may is not as simple and patients may also be over diagnosed
• Management options may be limited
Metabolic Disorders that may be treated by Liver Transplantations

- Maple Syrup Urine Disease
- Propionic Acidemia, Methyl Malonic Aciduria,
- Urea Cycle Disorders
- Primary Oxaluria (these patients may also require a kidney transplant)
- Certain types of Familial Hypercholesterolemia.