Pediatric Hepatology Potpourri

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Disclosure

• I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider of commercial services discussed in this CME activity

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Objectives

• To be able to recognize & manage patients with serious liver diseases that present with jaundice
• To be able to recognize & manage patients with serious liver diseases that present with hepatitis
Jaundice

- Jaundice is the yellowish discoloration of skin and mucous membranes
- An indication of an abnormality in Bilirubin metabolism
- Usually visible when levels are > 3mg/dl
- Bilirubin is produced mainly from RBC Hb
- Production rate is 6-8mg/kg/24hr in infants & 3-4mg/kg/24hr in adults
- Bilirubin is transported to the liver by albumin and conjugated to a more water soluble form

### Jaundice

Always obtain a fractionated Bilirubin i.e. Conjugated (Direct) & Unconjugated (Indirect)

<table>
<thead>
<tr>
<th>Unconjugated Hyperbilirubinemia</th>
<th>Conjugated Hyperbilirubinemia</th>
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</thead>
<tbody>
<tr>
<td>A- Increased bilirubin production</td>
<td>Abnormalities in excretion</td>
</tr>
<tr>
<td>B- Abnormalities in conjugation</td>
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</tbody>
</table>
Unconjugated Hyperbilirubinemia

*Increased Bilirubin Production*

- Blood group incompatibility
- RBC hemoglobinopathies
- Hematomas
- Polycythemia
- Drugs

Unconjugated Hyperbilirubinemia

*Conjugation Abnormalities*

- Breast Feeding Jaundice (Physiologic Jaundice)
- Breast Milk Jaundice
- Hypothyroidism
- Infants of diabetic mothers
- Medications and drugs

Unconjugated Hyperbilirubinemia

*Conjugation Abnormalities*

*Criggler Najjar Syndrome*

Hereditary deficiency of bilirubin glucuronosyl transferase (UGT1A1 gene)

- Type 1: Very high unconjugated bilirubin levels (20-40mg/dl). No response to phenobarbital
- Type 2: Medium elevation in unconjugated bilirubin levels (10-20mg/dl). Responds to phenobarbital
Unconjugated Hyperbilirubinemia

*Conjugation Abnormalities*

**Gilbert Syndrome**
- Most commonly presents in adolescents and adults
- Unconjugated bilirubin increases with fasting and illness
- ALT, AST, GGT, AlkP must be normal
- Treatment: None. Education

Conjugated Hyperbilirubinemia

*Excretion Abnormalities*

*Location of defect is the key to diagnosis*
*(hepatocyte, canaliculi, bile ducts)*
- Inborn errors of metabolism
  (Dubin Johnson Syndrome, Rotor Syndrome)
- Cholestasis syndrome (PFICs 1, 2, 3)
- Biliray Atresia
- Choledochal cyst
- Cholelithiasis

Other Causes of Jaundice

- Metabolic abnormalities
  *A1AT Deficiency, CF, Wilson’s, Tyrosinemia, Galactosemia*
- Infections
  *Hep A, B, C, CMV, EBV, Sepsis, UTI (newborn)*
- Drugs
  *Acetaminophen, Erythromycin, Valproate, Tetracycline, Statins, Insulin sensitizing agents*
- Toxins
  *Kava Kava, Amanita, heavy metals*
- TPN
Biliary Atresia

- Most common surgically correctable liver disease
- Incidence 1 in 15,000 births
- Etiology is unknown
- Progressive sclerosing inflammation of the biliary system
- Conjugated hyperbilirubinemia within the first few weeks of life

Biliary Atresia

- U/S may show absent GB and poor visualization of the CBD. Normal U/S doesn’t Rule it out
- May be associated with other anomalies i.e. Asplenia/polysplenia
- Dx: Imaging studies and liver Bx
- Operative correction may be helpful (Kasai procedure) must be done before 60 days
- Liver transplant is often required

Jaundice Work up

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT</td>
<td>Hepatocyte injury</td>
</tr>
<tr>
<td>GGT</td>
<td>Small bile duct injury &amp; metabolic Derangements</td>
</tr>
<tr>
<td>Alk P</td>
<td>Large bile duct obstruction</td>
</tr>
<tr>
<td></td>
<td>Difficult to assess in growing children</td>
</tr>
<tr>
<td>Albumin</td>
<td>Synthetic function. Long t½</td>
</tr>
<tr>
<td>PT/INR</td>
<td>Synthetic function. Short t½</td>
</tr>
<tr>
<td>Ammonia</td>
<td>Synthetic function</td>
</tr>
<tr>
<td>Clotting Factors V, VII</td>
<td>Synthetic function</td>
</tr>
</tbody>
</table>
Jaundice Work up

- Abdominal U/S
- CT scan
- MRCP
- ERCP
- Liver Biopsy

### Biliary Atresia
- Abdominal US, liver biopsy, cholangiogram

### Choledochal cyst
- Abdominal US

### A1AT deficiency
- A1AT level and phenotype

### IEOM
- Newborn screen (galactosemia)
  - Urine succinylacetone (tyrosinemia)
  - Serum amino acids, urine organic acids

### TORCH
- Urine CMV culture, TORCH titers

### UTI
- Urine Cx

### Cystic Fibrosis
- Newborn screen, sweat chloride test

### Alagille Syndrome
- Echocardiogram (if murmur present), spine film, ophthalmology exam, liver biopsy

### Hypothyroidism
- Newborn screen, TSH, total and free T4

### Pan-hypopituitirism
- TSH, total and free T4, early a.m. cortisol, glucose, brain MRI (assess pituitary gland)
Treatment

Depending on the cause
• Adequate nutrition
• Ursodeoxycholic acid
  (15-30 mg/kg/day divided BID)
• Fat soluble vitamins: ADEK
• Treatment for pruritus: Diphenhydramine,
  Hydroxyzine, Rifampin

Take Home Message

- Always obtain a fractionated Bilirubin
- Any Jaundice on DOL 1 is abnormal
- Any Conjugated Hyperbilirubinemia is abnormal
- Evaluation of Jaundice requires assessment of other aspects of liver function

Aminotransferases

• AST (SGOT): Found in liver, skeletal muscle, heart, kidney, brain, pancreas, lungs, WBC & RBC
  ➢ Present in both mitochondria (80%) & Cytosol (20%)
• ALT (SGPT): Localized to cytosol of hepatocytes only, relatively liver specific
Elevated Aminotransferases

- Elevation: ≥ 1.5 X upper limit of normal
- Minimal elevation: NASH
- Marked elevation:
  - Acute toxic injury i.e. Acetaminophen
  - Ischemic/Hypoxic
  - Acute viral disease
  - Alcoholic hepatitis

Causes of elevated aminotransferases

**Hepatic**

- Medications/Toxins
- Viral: Hepatitis A, B, C, EBV, CMV
- A1AT deficiency
- Autoimmune hepatitis
- Wilson’s disease
- Hemochromatosis
- Steatosis/NASH

**Non-Hepatic**

- Other AID: Celiac, IBD, SLE
- Thyroid disease
- Hemolysis
- Myopathy
- Acquired muscle disease
- Strenuous exercise
History & Physical

- Symptoms: Fever, jaundice, abdominal distension, pruritus, bleeding, fatigue
- FHx: Liver, AID (e.g. IBD, Celiac)
- PMHx: Blood transfusion, IV drugs, Foreign travel
- MedsHx: Herbal, Acetaminophen, Minocycline
- PE: HSM, liver edge, jaundice, ascites, portal HTN

Evaluation

- Drug/Toxin screen (Acetaminophen)
- Viral Serology (Hepatitis A, B, C, CMV, EBV, HSV, HIV, Adenovirus)
- Autoimmune markers: ANA, Total IgG, Anti-LKM, Anti-SM, Anti-F-Actin
- A1AT Pi typing
- Serum Ceruloplasmin, Serum copper, 24hr urine copper collection
- Serum Iron, Ferritin, TIBC

Evaluation

- Muscle: CK, Aldolase
- Other AID: Celiac panel
- Systemic: TSH/Free T4, ESR, CBC/diff
Evaluation

- Ab U/S (Liver, GB/Biliary system, Pancreas, Spleen)
- Doppler of hepatic vessels
- Ab CT scan
- ERCP
- MRCP
- **Liver Biopsy**
  (Histology, special stains, viral inclusions, presence & degree of fibrosis)

Alpha One Antitrypsin Deficiency

- AD with incidence of 1:800 live births
- 10-15% of CLD in children & adults
- Predisposes to lung & liver disease
- PiMM: normal (95%). PiZZ/PiSZ: severe deficiency, PiMZ: intermediate
- Clinically: First noted in the newborn period
- Treatment: None. Avoid smoking
  Supportive care. Liver transplant

Autoimmune Hepatitis

- Overall incidence 2:100,000
- 60-75% female, 40% <20yrs (10-14yrs)
- Wide range of presentation
- Two types
  - Type 1: ANA, SMA, F-Actin, P-ANCA
  - Type 2: LKM, Anti-liver cytosol
- Biopsy: Interface hepatitis, mononuclear infiltrate, piecemeal necrosis, plasma cells
- Treatment: **Prednisone, AZA, MMF, CSA,** Anti-TNF, IVIG, IL-2 ab, Rituximab, Liver Transplant
Wilson’s Disease (Hepatolenticular Degeneration)

- Rare AR with prevalence of 1:30,000
- Etiology: decreased hepatocellular excretion of copper into bile
- Variable presentation
  Classic 3: Liver disease, low Ceruloplasmin, Kaiser-Fleischer rings
- Treatment
  Chelating agents (D-Penicillamine, Trientine, Tetrathiomolybdate)
  Zinc, anti-oxidents, dietary avoidance, liver transplant

NAFLD/NASH

- NAFLD is the most common cause of liver disease in childhood and adolescence
  - A spectrum of liver pathology
    - A- Isolated steatosis or macrovesicular fat accumulation within hepatocytes without inflammation
    - B- NASH: fat accumulation associated with inflammation and/or evidence of cellular injury
    - C- Cirrhosis

NAFLD/NASH

- Predisposes to type 2 DM, HTN & dyslipidemia
- True Prevalence ?? (9.6 % in ages 2-19 yrs)
- Factors associated with increased risk
  - Obesity (10% are of healthy weight)
  - Male sex
  - Older age
  - Hispanic
  - Asian (esp. of Chinese and Filipino descent)
Pathogenesis

*Obesity (visceral adiposity) is correlated with dyslipidemia and increased insulin resistance*

- Two hit hypothesis:
  - Insulin resistance leads to hepatic steatosis
  - Oxidative injury required for progression to necroinflammatory steatohepatitis

Pathogenesis

- Presence of obesity in NAFLD increases risk of development of fibrosis 3 X
- Adolescent males more likely to develop NAFLD secondary to greater degree of insulin resistance in adolescents compared to children and adults. Estrogen may be protective

Diagnosis

- Age 10-14 yrs
- Mostly asymptomatic, some may have vague RUQ pain
  - Acanthosis Nigricans >50%
- Family Hx
- Initial labs: CBC, AST/ALT, GGT, Fasting lipid/glucose/insulin
Differential diagnosis

- Infections: HBV, HCV
- AIH
- Wilson’s
- A1AT
- Drug induced liver injury: Prednisone, Amiodarone, tetracycline, valproate, MTX
- Chronic TPN use
- Nutritional deficiencies: Refeeding syndrome, rapid weight loss/starvation
- Following bypass surgery

Imaging

**Hepatic U/S**

- Readily available & inexpensive
- Lack of sensitivity to milder degrees of steatosis, operator dependent, inability to adequately quantify the degree of steatosis, inflammation or fibrosis

**Hepatic MRI**

- More sensitive but more expensive

Liver Biopsy

- Dx: At least 5% of hepatocyte contain macrovesicular fat
- Types:
  - Type I: Steatosis with ballooning degeneration and perisinusoidal fibrosis
  - Type II: Steatosis with portal inflammation and/or portal fibrosis without ballooning degeneration
- Presence & degree of fibrosis
Treatment

- Weight loss through lifestyle modification
  - Elimination of foods high in saturated fats, trans fats and simple sugars
  - Increasing aerobic exercise
  - Decreasing sedentary behaviors
- Amount of weight loss is ??
- Pharmacological treatments
  - Metformin
  - Vitamin E

References

References

• Suchy FJ. Liver disease in children. 3rd ed. 2007
• Feldman et al. Sleisenger and Fordtran’s gastrointestinal and liver disease. 9th ed. 2010

Thank you
Questions ??