Liver Cases for the Primary Care Provider

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Disclosures

• I have no relevant financial relationships related to this presentation
Objectives

• Identify abnormal liver biochemical and function tests
  – Hepatocellular pattern
  – Cholestatic pattern
  – Isolated hyperbilirubinemia

• Identify when an urgent referral is needed
Outline

• Identification of liver injury
• History and exam
• Types of liver injury
• Differential diagnosis
• Lab evaluation
• Presentation of cases
• Summary
LFT’s

• “liver function tests”
• Doesn’t actually measure the function
  – Synthetic hepatic function
• Can be elevated in healthy livers
Liver labs

• Liver enzymes
  – Damage to the liver or biliary obstruction

• Serum albumin, PT/INR
  – Hepatic synthetic function

• Bilirubin
  – Measures the liver’s ability to detoxify metabolites and transport organic anions into bile
Liver enzymes

• Serum aminotransferases:
  – ALT: alanine aminotransferase (SGPT)
  – AST: aspartate aminotransferase (SGOT)

• Alkaline phosphatase
Reference range for serum alkaline phosphatase activity in children

Normal ranges for serum alkaline phosphatase activity for boys (blue) and girls (red).

Liver enzymes

• Serum aminotransferases:
  – ALT: alanine aminotransferase (SGPT)
  – AST: aspartate aminotransferase (SGOT)
• Alkaline phosphatase
• Gamma-glutamyl transpeptidase (GGT)
Evaluation of elevated serum alkaline phosphatase

- Rule out physiologic causes: pregnancy, postprandial increase (up to 1.5 to 2 X ULN), repeat fasting

**Determine the source**
- Gamma glutamyl transpeptidase or 5'-nucleotidase

- **Normal**
  - Alkaline phosphatase likely of bone origin
    - Evaluate for bone disorders

- **Increased**
  - Alkaline phosphatase likely of hepatobiliary origin
    - Right upper quadrant ultrasonography
      - Dilated bile ducts
        - MRCP or ERCP
          - AMA positive, ultrasonography normal or AMA negative, hepatic parenchyma abnormal
            - Liver biopsy
          - AMA negative and ultrasonography normal
            - Assess the degree of elevation of the alkaline phosphatase
              - ≥50 percent elevated
                - MRCP, ERCP, or liver biopsy
              - <50 percent elevated
                - Observation
      - No biliary ductal dilatation
        - Check AMA

AMA: antimitochondrial antibodies; ERCP: endoscopic retrograde cholangiopancreatography; MRCP: magnetic resonance cholangiopancreatography; ULN: upper limit of normal.
Liver enzymes

• Serum aminotransferases:
  – ALT: alanine aminotransferase (SGPT)
  – AST: aspartate aminotransferase (SGOT)
• Alkaline phosphatase
• Gamma-glutamyl transpeptidase (GGT)
• Lactate dehydrogenase (LDH)
Hepatic Synthetic Function

• PT/INR

• Elevated INR
  – Vitamin K deficiency
    • Prolonged jaundice
    • Intestinal malabsorption
  – Significant hepatocellular dysfunction

• Parenteral administration of Vitamin K
Hepatic Synthetic Function

• Serum albumin
  – Normal albumin ≈ acute process
  – Low albumin ≈ chronic process
History

- Infectious/Viral hepatitis
- Potential toxins
- Medical problems
- ROS
- Family History
Physical Examination

- Scleral icterus/Jaundice
- Spider nevi
- Palmar erythema
- Gynecomastia
- Caput medusae
- Neuro signs/symptoms

http://library.med.utah.edu/WebPath/LIVEHTML/LIVER061.html
http://medicalpicturesinfo.com/palmar-erythema/
Abdominal Examination

- Liver
  - Size
  - Consistency
- Ascites?
- Spleen?
- Mass?
Patterns of LFT abnormalities

• Hepatocellular
• Cholestatic
• Isolated hyperbilirubinemia
Patterns of LFT abnormalities

Hepatocellular
- Elevation in ALT and AST
- Bilirubin may be elevated
- Synthetic function +/- normal

Cholestatic
- Elevation in alk phos/GGT
- Bilirubin may be elevated
- Synthetic function +/- normal
Hepatocellular Pattern

- Broad differential
- Acetaminophen OD, drug reactions, toxin exposures
- Acute viral hepatitis
- Autoimmune hepatitis
- A1AT, Wilson disease
- Muscular disorders, seizures, heavy exercise
- NASH/NAFLD
- Other conditions: thyroid disorders, celiac, adrenal insufficiency
- Sepsis, Ischemia
Cholestatic Pattern

- Elevated alk phos
- Elevated GGT
- Intrahepatic
- Extrahepatic
Isolated Hyperbilirubinemia

• Fractionate the bilirubin
• Unconjugated (indirect) hyperbili
  – Overproduction
  – Impairment of uptake
  – Impairment of conjugation
• Conjugated (direct) hyperbili
  – Decreased excretion
  – Leakage
Indirect Hyperbilirubinemia

- Overproduction
  - Hemolysis
  - Extravasation
- Impairment of uptake
  - Drugs: rifampicin
  - Gilbert’s syndrome
  - Cardiac failure
- Impairment of conjugation
  - Gilbert’s syndrome
  - Crigler-Najjar (types I and II)
  - Neonates
  - Hyperthyroidism
Direct Hyperbilirubinemia

- Decreased excretion
- Leakage
- Isolated direct hyperbili in 2 rare conditions
  - Dubin-Johnson syndrome
    - Altered hepatocyte excretion of bilirubin
  - Rotor syndrome
    - Defective hepatic reuptake of bilirubin
Hepatology Work-up

- Acetaminophen level
- Toxicology/drug screen
- Viral hepatitis
  - HepA IgM Ab, HepB sAg and HepB cAb, HepC Ab (Hep C RNA)
  - HSV, Varicella, CMV, EBV, monosport
- Autoimmune hepatitis
  - ANA Ab, Anti-Smooth Mm Ab, Anti-LKM Ab, IgG level
Hepatology Work-up

- Alpha 1 antitrypsin deficiency
  - A1AT level and phenotype
- Wilson disease
  - Ceruloplasmin
- NASH/NAFLD
  - Cholesterol, triglycerides
- Muscular disorder/injury
  - CK level
Hepatology Work-up

• Thyroid
  – TSH, fT4 (thyroxine), +/- fT3RUQ US

• Celiac disease
  – TTG IgA and IgA level

• Adrenal insufficiency
  – Morning cortisol and ACTH

• Sepsis, bacteremia
  – UA, U Cx, Blood Cx
Hepatology Work-up

- RUQ US
- Liver biopsy
Cases

I heart guts.com
Case 1

• 12 day old male presented to PCP’s office for 2 week WCC
• MOC noted jaundice
• Solely breastfeeding, but felt to have good intake
• Weight is 1 oz below birth weight
Case 1

• Labs checked:
  – Total bili 13.7
  – Direct not checked

• Recommended admission for bili lights and formula supplementation

• MOC refused both, wanted to do bili blanket at home
Case 1

• 2 days later labs rechecked
  – Total bili 14.4
  – Direct bili 0.6
• 2 week old with visible jaundice
• Solely breastfeeding
• Labs confirm an indirect hyperbilirubinemia

Breast Milk Jaundice
Breast Milk Jaundice

- Jaundice that occurs within the first week of life and peaks within 2 weeks of life
- Progressively declines to normal levels over 3 to 12 weeks
- Results in excessive weight and fluid loss
- Different from breastfeeding failure
  - suboptimal intake or starvation related
Breast Milk Jaundice

- Thought to be due to a factor in human milk that promotes an increase in intestinal absorption of bilirubin
- Needs to be monitored to ensure that it remains unconjugated and does not increase
Case 2

- 17 yo male presented to Dermatology office for acne treatment
- Prior to starting therapy with isotretinoin, checked LFT panel
  - AST, ALT, alk phos normal
  - Total bili 3.1
  - Indirect bili 3.0
  - Direct bili 0.1
• Teenager with no signs or symptoms
• Routine lab check
• Low bilirubin elevation
  • Indirect/unconjugated

Gilbert’s Syndrome
Gilbert’s Syndrome

- Inherited gene mutation
- Unconjugated hyperbilirubinemia
- Benign
- Usually discovered incidentally
Gilbert’s Syndrome Signs

- Jaundice and/or scleral icterus

- Some conditions and situations may increase bilirubin levels:
  - Illness, such as a cold or the flu
  - Fasting or eating a very low-calorie diet
  - Dehydration
  - Menstruation
  - Stress
  - Strenuous exercise
  - Lack of sleep
Gilbert’s Syndrome

- Diagnosis is made by excluding other causes of unconjugated hyperbilirubinemia
- Genetic testing is available
- No treatment is necessary
- May be a risk factor for toxicity from some medications (such as chemotherapeutics and HIV meds)
Case 3

- 16 mo old male presented to ER with nausea, vomiting, abdominal pain
- Screening labs
  - AST 38, ALT 27
  - Total bili 0.4
  - Alk phos 10,954
- Normal KUB and abdominal US
Case 3

- Rechecked in a couple days
  - 7370
- Also sent alk phos isoenzymes
  - “Atypical pattern”
- Symptoms improving
• Toddler with acute gastroenteritis symptoms, now improving
• Normal ALT, AST, bilirubin
• Significantly elevated alk phos
• Isoenzymes: “in this sample, an atypical isoenzyme pattern was observed which makes quantification of fractions unreliable. This pattern is most likely due to Transient Hyperphosphataseemia, a typically benign condition. If clinically indicated consider sending another sample to repeat the analysis in 2-4 mo”

Transient Hyperphosphatasemia
Transient Hyperphosphatasemia

- Marked elevation of serum alkaline phosphatase in the absence of detectable liver or bone disease
- Usually 4-5 x uln, but up to 20 x uln
- More common <5 years old
- Benign
- Return to normal levels within weeks or months (usually 2-3 mo, but up to 6 mo)
Transient Hyperphosphatasemia

• Has occurred in association with a variety of clinical conditions, including gastroenteritis, respiratory infection, FTT, and asthma
• Needs thorough history and physical exam
  – Bone disease
  – Liver disease
  – Renal disease
  – Nonspecific symptoms including anorexia, weight loss, fever, and lethargy
  – Drugs
  – Nutritional rickets
Transient Hyperphosphatasemia

Testing

- AST, ALT
- Total and direct bilirubin
- GGT
- Calcium, phosphorus
- 25-hydroxyvitamin D
- Parathyroid hormone (PTH)
- BUN and creatinine
- Measurement of alkaline phosphatase isoenzymes by electrophoresis is usually not needed
  - The presence of excessive bone and liver fractions supports the diagnosis of TH and argues against primary hepatic or bone disease
Transient Hyperphosphatasemia

- Follow-up to document return of serum alkaline phosphatase levels to normal
- Consider repeating alk phos measurements every 6-8 weeks until a downward trend is noted and values normalize (or at least close)
- Sustained elevation beyond 3-4 months should prompt reconsideration of other causes of hyperphosphatasemia, including bone disorders
Case 4

• Full term infant, noted jaundice prior to discharge from the newborn nursery
• Eating well
• Growing well
• Yellow/green stools
• Parents note varying degrees of scleral icterus
Case 4

• PCP had been following labs due to jaundice
• 12 days old: T bili 7.9
• 13 days old: T bili 8, D bili 5.1, GGT 592, AST 45, ALT 117
• 23 days old: T bili 8.6, D bili 6.1, GGT 541, AST 222, ALT 75
• Normal A1AT phenotype PiMM and A1AT level 133
Case 4

- Ultrasound: normal liver and no focal liver lesions, gallbladder was visualized and appeared somewhat smaller and maybe contracted, no sludge or stones. There appeared to be a small CBD, without biliary dilation. Normal spleen, kidneys, and bladder.

- HIDA scan, pretreated with phenobarb: nonvisualization of the gallbladder and no GI activity at 4 hours and 24 hours images.
Case 4

• Other evaluation included work-up for possible Alagille syndrome
  – Ophtho examination for posterior embryotoxon: normal
  – Chest xray for vertebral anomalies: normal
  – ECHO for murmur: pulmonary valve stenosis
Case 4

- Patient underwent liver biopsy and cholangiogram at the age of 5 weeks
  - Findings: Fibrous remnant of a gallbladder, with no lumen and no bile ducts identified
  - Kasai portoenterostomy performed
Biliary Atresia

• Rare: 1 in 15,000-20,000
  – More common in AA and Asians than Caucasians
• Unsure of cause
• 10-15% of BA patients have other associated abnormality
Biliary Atresia Symptoms

• Appear 2-8 weeks after birth
• Prolonged jaundice
• Yellow or dark colored urine
• Pale/acholic stools
• Unusual bleeding (from umbilicus or nose)
Biliary Atresia Treatment

• Kasai procedure (AKA hepatopportoenterostomy)
Kasai procedure

http://uofmchildrenshospital.org/HealthLibrary/Article/88701
Biliary Atresia Treatment

• Kasai procedure (AKA hepatopportoenterostomy)
• Nearly half of all infants who have had a Kasai procedure require liver transplantation before age 5
• 85% of all children who have biliary atresia will need to have a liver transplant before they are 20 years old
• The remaining 15% have some degree of liver disease
• Some children may develop portal HTN and have GI bleeding, ascites and splenomegaly
Biliary Atresia

• Important things to remember from this case:
  – Patient did NOT have acholic stools
  – Ultrasound does NOT diagnose BA
  – The PCP was able to identify cholestasis early on by checking a direct bili when the total bili remained elevated
  – Better success with Kasai portoenterostomy when performed earlier in life (<60 days)
Case 5

- 11 yo male with abdominal pain
- Locally had a CT scan done noting “fatty infiltration of the liver”
- Other symptoms included vomiting, diarrhea/constipation
- He is obese with a BMI of 42
Case 5

• Screening labs:
  – Normal CMP except
  – ALT 94 (1.4 x uln)
  – AST 72 (1.2 x uln)

• Discussed weight loss

• Repeat labs still elevated

• Further liver evaluation
Case 5

- Abdominal US - Liver is mildly enlarged with diffuse increased echogenicity suggestive of fatty infiltration.
- A1AT PiMM with normal level
- Ceruloplasmin
- Autoimmune hepatitis panel
- HepBsAg, HepBsAb, HepBcAb
- Cholesterol and lipid panel
- Thyroid testing
- CK level
- HgbA1c
Case 5

• Hepatitis C antibody was positive

• Reminder that what looks like classic fatty liver disease, may not be

• HCV RNA qualitative testing was negative
  – either had a prior infection that subsequently cleared spontaneously, or
  – a false-positive antibody test
Likely NASH/NAFLD

• NAFLD: Non-alcoholic fatty liver disease
• NASH: Non-alcoholic steatohepatitis
• If transaminases remain elevated, will need a liver biopsy to confirm
NAFLD

- Currently no guidelines on screening
- Expert committee: biannual screening for liver disease with serum ALT and AST starting at age 10 years in obese children and those with BMI of 85th to 94th percentile with other risk factors
- Children that are not obese and found to have fatty liver (imaging), need to consider other causes:
  - Inborn errors of fatty acid or carnitine metabolism
  - Peroxisomal disorders
  - Lysosomal storage disorders
  - Wilson’s disease
  - Cystic fibrosis
NAFLD Treatment

• Lifestyle modifications, exercise, weight loss
• Vitamin E at 800 IU per day improves liver histology in non-diabetic adults with biopsy-proven NASH
  – AASLF practice guideline recommendations: Until further data is available, it is not recommended in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis
Case 6

• 13 yo F with referral for elevated transaminases
• One month prior she was seen by her PCP for nasal drainage, cough, intermittent sharp right sided abdominal pain, and plugged ears
• Dx with AOM and given Amoxicillin for a 10 day course
Case 6

- A few days after completion of the antibiotics, mom noticed that she had scleral icterus but thought it would resolve
- Over the next couple of weeks it would get better and worse, but never go away
- She had 2 episodes of vomiting over the previous couple of weeks
- Denied nausea, diarrhea, abdominal pain, weight loss, easy bruising/bleeding, joint pain, or rashes.
Case 6

- Mom requested that PCP obtain labs
  - ALT at 8 x ULN
  - AST at 15 x ULN
  - Total bilirubin of 2.3
  - Alk Phos at 1.3 x ULN
  - Protein of 10.4
  - Albumin of 2.7
Case 6

Normal labs
• Thyroid
• CK
• Hep A Ab, Hep B sAg, Hep B cAb, Hep C Ab
• CMV IgM Ab
• Ceruloplasmin: 21
• Celiac
• A1AT: 162 with MM

Abnormal labs
• IgG: 5690 (nml 759-1549)
• ANA: positive 1:80
  – Speckled pattern
• (LKM Ab: <1:10)
• Smooth Muscle Ab: positive at 1:1280
Case 6

• Ultrasound:
  – Coarse heterogeneously hyperechoic liver, indicating diffuse hepatocellular disease
  – Mild hepatomegaly
  – Moderate splenomegaly

• Liver biopsy:
  – Consistent with autoimmune hepatitis
• Female teenager
• Elevated liver transaminases
• Elevated protein:albumin ratio
• Elevated IgG
• Positive Smooth muscle Ab

Autoimmune Hepatitis
Type 1
Autoimmune Hepatitis

- Autoimmune
- Chronic - can lead to cirrhosis and liver failure
- Two types
  - Type 1 (classic): young women, can be associated with other autoimmune diseases
  - Type 2: less common, younger group (2-14 yrs)
Autoimmune Hepatitis Symptoms

- Usually minor
- Fatigue, abdominal discomfort, joint aches, pruritus, jaundice, hepatomegaly, nausea or spider angiomas on the skin
- Dark urine, loss of appetite, pale stools or absence of menstruation
- Severe complications can include ascites and mental confusion
- 10%-20% of cases present similar to an acute hepatitis
Autoimmune Hepatitis Treatment

- Prednisone
- Azathioprine (Imuran)
- 10-20% will progress to liver transplant
- Risk of recurrence after transplant
Case 7

• 2 mo old referred for cholestasis
• Full term, jaundice since birth
• At 5 days old: total bili 13.4
• Jaundice improved, but then worsened
• Fussy baby, didn’t eat well
Case 7

- Labs not checked again until 6 weeks old: total bili 5.4
- Rechecked at 7 weeks: Total bili 5.9, direct bili 4.1
- Rechecked at 8 weeks: Total bili 8.1, direct bili 4.3, ALT 200, AST 285
- Admitted to hospital for further evaluation
  - History obtained of whitish-gray stools
  - GGT 2030
Case 7

- Abnormal labs:
  - Alpha-1 antitrypsin low at 38, phenotype PI*ZZ
  - TSH 6
  - Urine positive for nitrates

- Ultrasound
  - Small contracted gallbladder with common bile duct visualized measuring within normal limits for size
  - Normal ultrasound appearance of the liver
Case 7

- HIDA scan: no excretion into the small bowel visualized at 24 hrs
- Repeat HIDA scan after 4 days on phenobarb: no excretion into the small bowel visualized at 20 hrs
- Cholangiogram: normal appearing gallbladder, visualization of bile ducts although small
- Liver biopsy: consistent with A1AT
Alpha-1 Antitrypsin Deficiency

• Patient’s cholestasis did not improve
• Liver transplant just before his first birthday
Alpha-1 Antitrypsin Deficiency

• Genetic disorder
• Low levels of A1AT
• Normal allele: M
• Abnormal allele: Z, variant S
• Normal MM
• Carrier MZ: mild to moderate deficiency
• Carrier MS: unclear of risk
• Deficient: SZ or ZZ: moderate to severe deficiency
Alpha-1 Antitrypsin Deficiency

- Lung disease in adults
- Liver disease at any age
- Can go undetected for years
- Cured only with liver transplant
End of Cases
Summary

• 2 patterns of elevated liver enzymes
  – Hepatocellular
  – Cholestatic

• Mild elevation of ALT/AST
  – Recheck labs, refer if persistently elevated
  – TSH/fT4, TTG/IgA, A1AT phenotype & level

• Jaundice/ scleral icterus/cholestasis
  – Refer immediately for further evaluation
Notes/Pearls

• Jaundice is pathologic if present in the first 24 hrs of life – needs URGENT evaluation!
• Patients with severe jaundice, or jaundice that persists after 1-2 weeks of age need further evaluation by PCP, including verifying NBS results, adequacy of intake, and stool color
• Any patient with elevated total bili needs to have a direct bili checked, and if elevated, needs referral
Notes/Pearls

• In infants/toddlers - it is karotenemia if there is NO scleral icterus AND palms are orange
• Not all elevated liver enzymes are due to a liver problem – look at the whole picture
When to refer

• Unexplained LFT elevation
• Persistent LFT elevation
• Direct hyperbilirubinemia
• Concerning physical exam findings (i.e. jaundice, hepatomegaly, etc)
References/Resources

- https://www.alpha1.org
- http://www.childliverdisease.org
- http://www.childrenshospital.org
- http://www.cincinnatichildrens.org
- http://www.gikids.org/
- http://www.liverfoundation.org
- http://www.mayoclinic.org
- http://www.uptodate.com
Thank you

Questions?