HEPATIC DISORDERS

I. ACUTE AND CHRONIC HEPATITIS

II. OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

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ACUTE HEPATITIS

- **Definition**: Acute inflammation of the liver, hepatocyte degeneration and necrosis
- **Time Course**: Less than 6 months
- **Spectrum of Disease**: Asymptomatic to fulminant liver failure
NEONATAL HEPATITIS

- **Definition**: Acute inflammation of the liver within the first one month of life

**Etiology: Infection**

- Viruses
  - TORCHES
- Adenovirus, ECHO virus, Coxsackie virus
- May present as fulminant liver failure
Presentation:

- At birth or first few days of life
- May be SGA
- May present as sepsis
NEONATAL HEPATITIS

Diagnostic Clues:
- Enlarged liver, spleen, rashes

Characteristic Laboratory Findings:
- ↑ AST/ALT ± ↑ conjugated bilirubin
- ↓ platelets, WBCs ↑↓ or normal
NEONATAL HEPATITIS

Etiology: Metabolic

- Tyrosinemia, galactosemia, fructosemia may present as fulminant hepatitis

- **Diagnostic clues**
  - galactosemia: reducing substances in urine
  - fructosemia: liver failure after introduction of fruit juices
  - tyrosinemia: succinylacetone in urine
NEONATAL HEPATITIS

Metabolic: Alpha-1 antitrypsin deficiency

- ↑ conjugated bilirubin with ↑ AST/ALT
- jaundice often resolves in first 6 months
- rarely a cause of significant liver disease in infancy
- Key Diagnostic Test: Alpha-1 antitrypsin level in serum, genotype ZZ
NEONATAL HEPATITIS

Metabolic: Neonatal hemochromatosis

- Abnormal iron deposition in liver and other organs
- May present with fetal hydrops, profound cholestasis and early death
- Variable familial inheritance
- Cause: maternal antibody attacks fetal hepatocytes
  - Gestational alloimmune liver disease
- Key Diagnostic Tests: ↑ iron, ↑ ferritin, MRI of abdomen
ACUTE HEPATITIS - CHILDHOOD

Etiology: Infection

Hepatitis A:

- RNA virus
- **Incubation**: 15-20 days
- **Spread**: fecal - oral
- **Risk factors**: poor hygiene, contaminated food and water
ACUTE HEPATITIS - CHILDHOOD

Hepatitis A:

- **Presentation**: variable, from anicteric form to fulminant liver failure
- **Peak age**: incidence 5-14 years, children more likely to be asymptomatic compared to adults
- **Anorexia**: low grade fever, RUQ pain
- **Physical exam**: ± jaundice, ↑ liver size
Hepatitis A:

- **Key Diagnostic Tests:** ↑ AST/ALT > 1,000 ± hyperbilirubinemia
- **Beware of coagulation defects and** ↑ serum ammonia, low serum glucose
- **Outcome:** excellent, no chronic disease
  - < 1% fulminant hepatitis
ACUTE HEPATITIS - CHILDHOOD

Hepatitis A: Serologic diagnosis

Hepatitis A viral antibody, IgM fraction ↑
Hepatitis A total antibody or IgG antibody does not differentiate acute from past infection or vaccination

- **Treatment**: symptomatic
- **Prevention**: hepatitis A vaccine, immune globulin
Hepatitis A Infection
ACUTE HEPATITIS - CHILDHOOD

Hepatitis B:

- DNA virus
- **Incubation:** 50-60 days
- **Spread:** blood, saliva, sexual contact
  - intrafamily, and perinatal
- **Risk factors:** contaminated blood, needles, carrier mother
ACUTE HEPATITIS - CHILDHOOD

Hepatitis B:

- **Presentation**: spectrum from anicteric, asymptomatic disease to fulminant liver failure
  - asymptomatic chronic carrier state common
- **Symptoms**: malaise, low grade fever, RUQ pain
- **Extra-hepatic associations**: common
Hepatitis B:

- **Clinical course:** 90% of infected neonates will not clear hepatitis B antigen and become chronic carriers
  - 90% of adults acquiring hepatitis B WILL clear the virus
- **Chronic carrier state:** associated with chronic active hepatitis, cirrhosis, hepatocellular carcinoma
ACUTE HEPATITIS - CHILDHOOD

Hepatitis B:

- **Sero logic diagnosis**
  - acute infection: ↑ HB surface antigen
  - ↑ HBE antigen
  - if virus cleared HB surface antibody becomes positive, the only **protective antibody**
  - hepatitis B core antibody rises early in course of infection
  - IgM component early
  - IgG component late
Acute Hepatitis B Infection
Viral Clearance
**ACUTE HEPATITIS - CHILDHOOD**

**Hepatitis B:**

- **Treatment:** symptomatic
- **Prevention:** vaccination newborns
  - passive immunization, hepatitis B immunoglobulin
- Newborn infant of carrier mother should receive both active and passive immunization
Hepatitis C:

- RNA virus
- **Incubation:** 40-60 days
- **Spread:** parenteral, perinatal, unknown
- **Risk factors:** blood transfusions, IV drug abuse
  - 50% of cases no risk factor identified
Hepatitis C:

- **Presentation:** acute disease usually asymptomatic
  - chronic disease occurs in up to 75% of infections
  - half of which progress to chronic hepatitis
  - risk for cirrhosis and hepatocellular carcinoma
ACUTE HEPATITIS - CHILDHOOD

Hepatitis C: Serologic diagnosis

- Hepatitis C viral antibody not protective
- Hepatitis RNA by PCR indicates antigen viremia
- **Treatment:** symptomatic
  - ‘Standard’: interferon and ribavirin
  - ‘New – adults only
  - Combinations of direct acting antivirals
  - Sofosbuvir + ledipasvir – 90% ‘cure’
  - Oral, short course, no interferon
**Delta hepatitis:**

- Unclassified virus
- Occurs only with co-infection with hepatitis B
- Higher prevalence in Eastern Europe, Mediterranean
- **Diagnosis:** IgM antibody to HDV
Viral hepatitis E:

- RNA virus
- **Incubation:** 3-9 weeks
- Epidemics with contaminated water
- Endemic disease also present in developing countries
- **Clinical presentation:** similar to hepatitis A, no chronic disease
- **Diagnosis:** IgM antibody detection
Other infections: Other acute viral infections of childhood may also infect the liver

- CMV, EBV, herpes 1 virus, varicella
- EBV virus may cause ↑AST/ALT and jaundice
  - liver and spleen enlarged with adenopathy characteristic
- CMV, herpes, varicella important in immuno-compromised children
ACUTE HEPATITIS - CHILDHOOD

Etiology: Toxic and Metabolic

Drug Toxicity:
● Accidental overdose acetaminophen may cause fulminant liver failure
● Other commonly associated drugs causing hepatitis
  – antituberculous drugs e.g. INH
  – anticonvulsants sodium valproate
  – halothane
  – antineoplastic drugs e.g. methotrexate, 6MP
ACUTE HEPATITIS - CHILDHOOD

Drug Toxicity:

- Presentation: highly variable
- Characteristic injury with acetaminophen overdose
  - ↑ AST/ALT, mild elevation of bilirubin, ↑ PT/INR, ↑ ammonia
  - presents as fulminant liver failure
- Specific treatment: N-acetyl cysteine
ACUTE HEPATITIS - CHILDHOOD

**Ingestions:**
- Mushrooms most common: *amanita phalloides*

**Reye and Reye-like syndromes:**
- Unknown etiology, ? mitochondrial defect
- Associated with aspirin use and varicella
- Presents as fulminant liver failure with cerebral edema
ACUTE HEPATITIS - CHILDHOOD

Toxic metabolic - Environmental toxins:

- Glue sniffing, polyvinyl alcohol, CCL$_4$
- Presentation: variable
  - fulminant liver failure
  - chronic active hepatitis
  - cholestasis
CHRONIC HEPATITIS - CHILDHOOD

Chronic hepatitis:
- **Definition:** Chronic inflammation of the liver of > 6 months duration
CHRONIC HEPATITIS - CHILDHOOD

**Etiology:** Infections - Hepatitis B and C

- Clinical features similar
- Gradual onset
- Histology varies from persistent hepatitis to cirrhosis
- **Presentation:** features of chronic liver disease
  - malaise, jaundice, encephalopathy, ascites, portal hypertension, weight loss
- May be surprisingly asymptomatic even with cirrhosis
CHRONIC HEPATITIS - CHILDHOOD

Diagnosis: Serology

- Physical exam: small shrunken liver ▲ spleen, clubbing, ascites, spider angiomata, malnutrition, encephalopathy

- Management - symptomatic:
  - fluid and sodium restriction
  - treatment of encephalopathy
  - transplantation
CHRONIC HEPATITIS - CHILDHOOD

Laboratory findings:

- AST/ALT may be increased generally < 500 IU/ml
  - conjugated hyperbilirubinemia,
  - however bilirubin and/or AST or ALT may be normal even with cirrhosis
  - poor synthetic function (i.e. ↑ PT, ↓ albumin)
CHRONIC HEPATITIS - CHILDHOOD

Hepatitis B: Chronic carrier state

- HB surface antigen positive, no HB surface antibody
- E antigen and E antibody variably present
- If hepatitis E antigen positive or DNA PCR positive: indicates viral replication
- Hepatitis B core antibody IgG, persists
Chronic Hepatitis B

Relative level

- Incubation: 1-3 months
- Acute infection: 6 months
- Chronic infection: Years

Relative time

- HBsAg
- Total Anti-HBc
- HBeAg
- Anti-HBc IgM

*HBeAg indicates active replication
CHRONIC HEPATITIS - CHILDHOOD

Treatment: when to treat?

Hepatitis B:
- Interferon alone
- Antiviral therapy alone – lamivudine: problem is resistance
- ??Combination therapy

Hepatitis C
- Interferon and ribavirin – better sustained response rate than in adults
CHRONIC HEPATITIS - CHILDHOOD

Metabolic: Alpha-1 antitrypsin deficiency:

- Associated with ZZ phenotype
- Liver disease presents in childhood, lung disease in late childhood or adulthood
- Cirrhosis with portal hypertension most common presentation
- **Treatment:** none
  - if end-stage liver disease, liver transplantation indicated
CHRONIC HEPATITIS - CHILDHOOD

Metabolic: Cystic Fibrosis

- Cirrhosis and portal hypertension usually occur in mid-childhood
- Liver disease may be more severe than lung disease in some children
- May progress to cirrhosis
- **Treatment:** portal hypertension
  - shunt procedure
  - liver transplantation – lung transplantation
CHRONIC HEPATITIS - CHILDHOOD

Metabolic: Wilson’s disease

- Defective copper metabolism
- Accumulation of copper in liver, CNS, kidney
- **Characteristic laboratory findings:**
  - ↓ serum copper
  - ↓ serum ceruloplasmin
  - ↑ 24 hour urine copper
  - ↑ liver copper content on biopsy is diagnostic
Metabolic: Wilson’s disease

- **Presentation:** highly variable
  - acute fulminant hepatitis: hemolytic anemia crisis common
  - chronic active hepatitis ± cirrhosis with portal hypertension
  - asymptomatic, ↑AST/ALT only

- **Neurologic symptoms:** may be subtle
  - changes in personality, school performance
  - look for Kayser-Fleischer rings
CHRONIC HEPATITIS - CHILDHOOD

Metabolic: Wilson’s disease

- **Treatment:** if no cirrhosis or no fulminant liver failure chelating agents
  - Penicillamine, trientene
  - if cirrhosis or fulminant liver failure transplantation only option

- **NB:** screen family members
CHRONIC HEPATITIS - CHILDHOOD

**Metabolic: Tyrosinemia**

- Autosomal recessive
- May present as fulminant liver disease in infancy or chronic disease in childhood
- Hepatocellular carcinoma develops in the majority before age 3 years
- Neurologic crisis and renal impairment common
CHRONIC HEPATITIS - CHILDHOOD

Metabolic: Tyrosinemia

Treatment:
- dietary management
- NTBC - stops tyrosine degradation
- ?? Stops HCC risk
- Incidental HCC indication for liver transplantation
CHRONIC HEPATITIS - CHILDHOOD

Progressive Familial Intrahepatic Cholestatic diseases:

- Defect of bile acid metabolism/excretion
- May mimic chronic hepatitis
- Variable histology
- Familial syndromes common
- Clinical presentation often with cholestasis, pruritus
- Non-specific inflammation of liver may progress to fibrosis and cirrhosis in some
- **Treatment:** symptomatic especially for pruritus
  - liver transplantation occasionally indicated
CHRONIC HEPATITIS - CHILDHOOD

**Parenteral nutrition induced:**

- Etiology poorly understood
- Chronic inflammation progresses to fibrosis and cirrhosis
- Most often occurs when enteral feedings are minimal
- **Management:** ↑ enteral feedings as much as possible
  - liver transplantation sometimes indicated
  - Role of omega -3 rich intralipid
CHRONIC HEPATITIS - CHILDHOOD

Autoimmune:

- Most often presents in adolescent females, however may occur any age, any sex
- Presentation: variable
  - chronic liver disease with chronic active hepatitis, cirrhosis, portal hypertension
  - subacute fulminant liver failure
CHRONIC HEPATITIS - CHILDHOOD

Autoimmune:

- Diagnostic clue: high serum protein with low serum albumin indicating hypergammaglobulinemia
- Autoimmune diagnostic markers may be positive
CHRONIC HEPATITIS - CHILDHOOD

Autoimmune:

- **Treatment:** immunosuppression
  - steroids, 6MP, or azathioprine
- **Look for other organ involvement**
  - arthralgia, arthritis, rashes, ulcerative colitis, Crohn’s disease, diabetes mellitus, etc.
Cryptogenic:

- Etiology not determined
- Role of steatohepatitis
- May progress to end-stage liver disease
- May require liver transplantation
Obstructive Jaundice Beyond the Neonatal Period
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Biliary Atresia:

- Occurs in 1:10,000-14,000
- Presents in full-term infants with conjugated hyperbilirubinemia within the first 4 weeks of life
- **Classic form:** complete atresia of external biliary system, ongoing liver fibrosis and eventual cirrhosis
- Without biliary drainage procedure progression to end-stage liver disease and death inevitable within 1-2 years of life
Biliary Atresia
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Biliary Atresia:

- Early diagnosis essential: jaundice beyond the first 2 weeks must be investigated
- Hyperbilirubinemia is conjugated
- All cases of conjugated hyperbilirubinemia in this age range must have biliary atresia ruled out
- If biliary drainage procedure delayed beyond 3 months of age < 25% will achieve short-term success
Biliary Atresia
Kasai Procedure
Roux-en Y hepatico jejunostomy
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Biliary Atresia:

- Even with biliary drainage 75% of children will require liver transplantation
- Progression of disease highly variable
- Cirrhosis even with biliary drainage procedure may occur within first year of life or be delayed until childhood
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Biliary Atresia:

- Indications that biliary drainage is failing
  - recurrence of cholangitis
  - recurrence of jaundice
  - development of portal hypertension and cirrhosis
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Paucity of the intrahepatic bile ducts:

- Intrahepatic bile ducts are either absent or very few
- In syndromic form: Alagille's syndrome
  - association with congenital heart disease especially pulmonary stenosis
  - also short stature, triangular facies, butterfly vertebrate
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Paucity of the intrahepatic bile ducts:

- Presents as cholestasis and pruritus
- Synthetic function usually preserved
- Symptomatic treatment may be all that is required
- A few require liver transplantation
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Choledochal Cyst:

- Typical presentation: female, school-aged, child
- Abdominal mass, RUQ pain, intermittent jaundice, fever
- Conjugated hyperbilirubinemia
- Diagnosis on ultrasound
- Surgical correction possible in the majority
Choledochal Cyst
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Sclerosing Cholangitis:

- **Definition:** Chronic inflammation causing focal areas of fibrotic narrowing and dilation of the intra and extrahepatic bile ducts
Sclerosing Cholangitis
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Primary Sclerosing Cholangitis:

- Relatively rare in children, associated with ulcerative colitis
- **Presentation:** fever, abdominal pain,
  - < 50% have jaundice
- Liver enlarged possibly also spleen
- **Diagnostic exam:** the cholangiogram
  - ERCP
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Primary Sclerosing Cholangitis:

- **Laboratory findings:** ↑ serum bilirubin occasionally AST/ALT
  - impressive elevation of alkaline phosphatase and GGT
- **Treatment:** symptomatic
- **Prognosis:** may progress to end-stage liver disease, cholangiocarcinoma
  - may require liver transplantation
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Secondary Sclerosing Cholangitis:

- Most often seen with autoimmune and immunodeficiency syndromes
- Associated with inflammatory bowel disease
- Langerhan’s cell histiocytosis
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Cholelithiasis:

- Etiology usually unknown
- Rule out hemolytic disorders, cystic fibrosis
- Other associations: primary liver disease, ileoresection, obesity, family history of gallbladder disease, parenteral nutrition
- < 6% occlude cystic or common bile duct
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Cholelithiasis:

- **Symptoms:** intermittent abdominal pain ± jaundice
- If stones migrate to common bile duct causes: obstruction, cholangitis, intrahepatic abscesses, pancreatitis
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

**Cholelithiasis:**

- **Laboratory findings:** may show only ↑ alkaline phosphatase
- **Treatment:** exclude contributing factors, try ursodeoxycholic acid
- Elective cholecystectomy
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Cholecystitis:

- **Definition:** acute or chronic inflammation of the gallbladder with or without stones
- **Calculus cholecystitis:** impaction of stone in cystic duct
- **Bacterial infection supervenes e.g.** E-coli, enterococcus
- Most often in females
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Cholecystitis:

- **Clinical presentation:** colicky, RUQ pain, referred to right scapula
  - fever, jaundice
- **Diagnosis:** ↑ bilirubin and alkaline phosphatase
  - ultrasound or biliary isotope scan
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Non-calculus cholecystitis:

- No stones in gallbladder
- May be seen after systemic infection e.g. enteric infections: salmonella, shigella
- Congenital abnormalities of gallbladder
- **Clinical features and management:** same as calculus cholecystitis
- **Treatment:** cholecystectomy once inflammation has settled
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Pancreatitis:

- Pancreatitis may cause cholestasis secondary to edema and compression of common bile duct
- Progressive fibrotic pancreatitis may encase bile duct
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Pancreatitis:

- Clues that pancreatitis is underlying course of cholestasis
  - epigastric pain with vomiting, ↑ amylase and lipase
  - enlarged pancreas on imaging of abdomen
- Chronic pancreatitis more difficult to diagnose, serum amylase/lipase may be normal
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Biliary Obstruction External to the Biliary System:

Tumors:

- Primary liver tumors of childhood usually parenchymal and do not cause jaundice
- Hepatoblastoma most common, hepatocellular carcinoma rare
- Neuroendocrine tumors, sarcomas may cause external compression of bile duct causing jaundice
Hepatoblastoma
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Abscesses and Cysts:

- Unusual cause of jaundice unless impinging on porta hepatis
- Abscesses within liver, consider amoebic abscess, echinococcal cysts and hepatic abscess from intra-abdominal infection
- Benign hepatic tumors: adenomas, hamartomas, focal nodular hyperplasia
Echinococcal Cyst
OBSTRUCTIVE JAUNDICE BEYOND THE NEONATAL PERIOD

Abscesses and Cysts:

- Diagnosis imaging studies, ultrasound, CT, MRI, angiography
- Management resection
  - liver transplantation if resection not possible
- Small benign tumors no therapy
- Large abscesses: drain and excise
Children are the living messages we send to a time we will not see

N Postman