Chronic hepatitis in children

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Hepatitis is a term for inflammatory diseases of the liver, grossly subdivided into infectious and noninfectious, which are characterized by a wide variety of clinical and histologic manifestations, ranging from mild and self-limited to severe and progressive forms leading to liver failure, cirrhosis, or hepatocellular carcinoma.

Acute/Chronic hepatitis means ongoing inflammation of the liver persisting for **less/more than six months** that is detectable by biochemical and histologic means

Causes of hepatitis

- Viral hepatitis
  - A, B, C, D, E, F, G…
  - HSV
  - CMV
  - EBV
  - HIV
  - Rubella
  - Adenoviruses
  - Enteroviruses
- Drug-induced hepatitis
  - Nonsteroidal anti-inflammatory drugs (acetaminophen, ibuprofen, diclofenac)
  - Antibiotics (Erythromycin, Tetracyclines, Amoxicillin-clavulanate)
  - Antituberculosis drug (isoniazid , rifampicin, pyrazinamide)
- Autoimmune hepatitis
  - anti-smooth muscle auto-antibodies
  - endoplasmatic antireticulum auto-antibodies
  - anti-cytosol auto-antibodies
  - hepatitis with gigantic cells
  - infant autoimmune hemolytic anemia
- Metabolic-genetic hepatitis
  - Wilson's disease
  - cystic fibrosis
  - α1-antitrypsin deficiency
  - haemochromatosis
  - glycogen storage dsease type IV

Clinical evolution of hepatitis

- Acute evolution
- Acute malignant (fulminant)
- Chronic evolution

Chronic hepatitis classification

- Old classification
  - Chronic persistant hepatitis
  - Chronic active hepatitis

Based on histopathological distinction

- Present classification

- Cause
- Grade
- Severity

Grade of chronic hepatitis

Histological assessment of necroinflammatory activity

- Portal inflammation
  - Periportal necrosis
  - Piecemeal necrosis or interface hepatitis
- Bridging necrosis

Severity of chronic hepatitis

- Level of progression of the disease based on the degree of fibrosis or cirrhosis

KNODELL score

0. NO fibrosis
1. Fibrous portal expansion
3. Bridging fibrosis (portal-portal or portal-central linkage)
4. Cirrhosis

Los Angeles classification (1994)

1. Chronic viral hepatitis B, C, D, G, F…
2. Autoimmune hepatitis
3. Drug hepatitis
4. Cryptogenic hepatitis

4 Phases

1. Replication
2. Integrating B-VHB-DNA / D,C VHD-RNA / VHC-RNA
3. Acutisation
4. Remittency

Burden of viral hepatitis

- The problem of viral hepatitis remains the urgent, as these diseases takes the third place after acute respiratory and acute intestinal infections as to its spreading.
- Viral hepatitis is a most frequent cause of chronic hepatitis and liver cirrhosis.
- In some patients viral hepatitis may have lethal outcome.
- Hepatotropic viruses have little in common from a virology standpoint other than that they infect the same organ.
- In general, the symptoms result from the body's immune response, not infection itself.
- The key differences are:
  - Transmission route
  - Incubation period
  - Clinical manifestations
  - Availability of a vaccine
  - Treatment
  - Outcomes

Clinical Spectrum

- **Subclinical Infection** – serologic and biochemical evidence of infection but asymptomatic
- **Clinical Infection** – signs and symptoms of hepatitis
  - Acute fulminant – massive necrosis
  - Acute self-limited – complete recovery
  - Chronic carrier – usually non-progressive
  - Chronic active – progressive damage +/- symptoms
    - ✓ Cirrhosis and liver failure
    - ✓ Hepatocellular carcinoma

Chronic Viral Hepatitis B – Key facts

- Hepatitis B is a viral infection that attacks the liver and can cause both acute and chronic disease
- The virus is transmitted through contact with the blood or other body fluids of an infected person
- Hepatitis B virus is 100 times more infectious than the HIV virus
- An estimated 257 million people are living with hepatitis B virus infection (defined as hepatitis B surface antigen positive)
- In 2015, hepatitis B resulted in 887 000 deaths, mostly from complications (including cirrhosis and hepatocellular carcinoma)
- Chronic hepatitis B is usually diagnosed as a result of a workup for abnormal liver function tests or as a result of screening patients at risk for HBV infection
- Many patients with chronic hepatitis B have no symptoms or have nonspecific symptoms such as fatigue or right upper quadrant discomfort
- However, it can be prevented by currently available safe and effective vaccine

Transmission routes of HBV

- HVB virus can survive outside the body for at least 7 days
  - During this time, the virus can still cause infection if it enters the body of a person who is not protected by the vaccine.
- **Incubation period** of hepatitis B virus is 75 days on average, but can vary from 30 to 180 days
  - The virus may be detected within 30 to 60 days after infection and can persist and develop into chronic hepatitis B
- **Perinatal transmission** – from mother to child at birth
- **Horizontal transmission** (exposure to infected blood), especially from an infected child to an uninfected child during the first 5 years of life
- **Percutaneous or mucosal exposure** to infected blood and various body fluids, as well as through saliva, menstrual, vaginal, and seminal fluids
- Infected HBsAg blood during **transfusion** (until 1970)

Chronic Hepatitis B Infection in Pediatrics

- Mostly asymptomatic
- Normal growth
- Liver damage mild during childhood
- Cirrhosis, hepatocellular carcinoma at any age

Natural History of Chronic HBV in Pediatrics

- HBeAb seroconversion rate 55% in 12 years
- Lower seroconversion in vertical transmitted (38.5%) vs. horizontal (74%)
- Loss of HBsAg seen in 5%

Diagnostic Interpretations of Hepatitis B markers

HBsAg	Non infectious component of viral coat	Indicator of disease. If > 6 months: chronic HBV
Anti-HBs	Antibody response to HBsAg	Indicates recovery and/or immunity
HBeAg	Antigen that correlates with replication and infectivity	High level of infectivity and replication
Anti-HBe	Antibody response to HBeAg	Decreasing level of replication Remission/resolution
Anti-HBc IgM	Non protective antibody to the HBcAg	Recent HBV infection
Anti-HBc IgG	As above	Acute or remote exposure to HBV
HBV DNA	Replictative genetic material of HBV; infectious agent	Viral replication and continues infection

Who to treat?

- Children with chronic HBV (HBsAg > 6 months)
- Children born from mothers with acute or chronic VHB or carrier of HBsAg, must be followed at 2, 3, 6, and 12 month after their discharge fromn the hospital (transaminase activity and blood markers are done after 6 month)
- Indications
  - Cytolysis >> 2 x normal values > 12 month
  - Liver biopsy – necrosis, marked inflammation, reduced fibrosis
  - HBeAg + and/or VHB DNA +
  - Functional immune system (no primary or secondary immunodeficiency)
  - No cardiac, renal, immune failures, healthy mental status
- Better Response to treatment
  - High ALT
  - Inflammation in biopsy
  - Low HBV DNA
  - Late acquisition of infection

Contraindications and treatment precautions

Contraindications

- Hepatic decompensation
  - albumin <3.0 g/l
  - bilirubin >51.3 μ mol/l (30 mg/l)
  - prolonged prothrombin time >3.0 s
- Portal hypertension: variceal bleeding, ascites, encephalopathy
- Hypersplenism
  - leukopenia (<2 x 109/l)
  - thrombocytopenia (<7 x 107/l)
- Psychiatric depression: severe, suicide attempt
- Autoimmune disease: polyarteritis nodosa, rheumatoid arthritis, thyroiditis
- Major system impairment: cardiac failure, obstructive airways disease, uncontrolled diabetes
- Pregnancy
- Current intravenous drug abuse
- Hypersensibility to IFN-α

Precautions

- Monthly tests: full blood count, bilirubin, ALT, AST, GGT, blood coagulation
- Once in 3, 6, 9 month, 1, 2, and 4 years: HBeAg, DNA VHB viral load
- Once in 6, 12 month: abdominal ultrasound (Doppler in hepatosplenomegaly or portal hypertension signs)

Treatment

- IFN-α (Intron A)
  - Approximative 58% of patients show response
  - Side effects: flu-like symptoms, fatigue, arthralgia, headache, depression
- Lamivudine
  - Virologic response in children - 23%
  - Increased risk of drug resistant, 70% by 5 years
- Entecavir
- Adefovir

Prevention of Hepatitis B

- Universal precautions
  - Obligatory examination of blood donors for HBsAg detection
  - Prohibition of hemotransfusion and use of blood derivatives marked positive for HBsAg
  - Use of disposable instruments
  - Education (needles, sex)

- Hepatitis B Immunoglobulin (HBIG)
  - May be used to protect persons who are exposed to hepatitis B
  - It is particular efficient within 48 hours from the moment of incident
  - It may also be given to neonates whose mothers are HBsAg and HBeAg positive
- Hepatitis B vaccine (HepB)
  - 1965 – discovery of hepatitis B virus ("Australia Antigen", now HBsAg)
  - 1971 – developing a blood test for the hepatitis B, used by blood banks to screen donors → decreased VHB risk transfusion 25%
  - 1981 – FDA approved plasma-derived hepatitis B vaccine ("inactivated" type of vaccine), discontinued in 1990
  - 1986 – genetically engineered (or DNA recombinant) hepatitis B vaccines
  - A primary 2 to 3-dose series induces protective antibody concentrations in >95% of healthy infants, children and young adults

Hepatitis C "transfusion related non-A, non-B hepatitis"

- **No vaccine available**
- 6 genotypes worldwide, many subtypes and isolates based on nucleotide diversity
- Genotype does not influence disease progression but does affect response to antiviral treatment (Genotypes 2 and 3 more responsive to alpha-interferon therapy than Genotype 1)
- Affects each person differently
- Usually asymptomatic or mild disease
- Chronic infection very common
- 20% of community acquired hepatitis
- 90% post-transfusion hepatitis (prior to 1992)
  - Blood banks started screening in 1992: <1% risk now

Mode of transmission

- Vertical (most important among children)
- Use of intravenous drugs
- Sexual
- Transfusion of blood or contaminated products (prior to 1992)

Perinatal Transmission of Hepatitis C

- 3.7% of the infants acquired HCV
- Infection rate in HIV positive mothers, 25%
- Role of viral titer unclear
- Infected infants do well – severe hepatitis is rare

Risk Factors for Vertical Transmission of Hepatitis C

Does not increase vertical transmission

- Breast feeding
  - HCV detected in breast milk and colostrum
  - Rate of transmission identical to bottle-fed infants
  - Safety based on the absence of traumatized, cracked or bleeding nipples
- Delivery method

Does increase vertical transmission

- Use of internal fetal monitoring devices
- High viral loads
- Prolonged rupture of membranes (>6 h)
- HIV co-infection

Clinical Features of VHC in Pediatrics

- Normal growth
- Mostly are asymptomatic
- Hepatomegaly 2-61%
- Elevated liver enzymes 44-93%

Hepatitis C Diagnosis

- Symptoms
- Elevated level of liver enzymes
- Rule out other causes of hepatitis
- Confirmed by serology
  - Serologic test detects HCV antibody
  - Positive in chronic cases
  - May not be positive in acute phase
  - Rule out other causes of acute hepatitis

Laboratory Diagnosis

- HCV antibody
  - generally used to diagnose hepatitis C infection
  - not useful in the acute phase as it takes at least 4 weeks (10-30 weeks) after infection before antibody appears
- HCV-RNA
  - various techniques are available e.g. PCR and branched DNA
  - may be used to diagnose HCV infection in the acute phase
  - however, its main use is in monitoring the response to antiviral therapy
  - HCV-RNA disappear after 6 month of treatment in 50-95%
- HCV-antigen
  - an EIA for HCV antigen is available
  - it is used in the same capacity as HCV-RNA tests but is much easier to carry out

Biochemical Indicators of Hepatitis C Virus Infection

- In chronic hepatitis C, increases in the alanine and aspartate aminotransferases range from 0 to 20 times (but usually less than 5 times) the upper limit of normal
- ALT levels are usually higher than AST levels, but that finding may be reversed in patients who have cirrhosis
- Alkaline phosphatase and gamma glutamyl transpeptidase are usually normal, if elevated, they may indicate cirrhosis
- Rheumatoid factor, low platelet and white blood cell counts are frequent in patients with cirrhosis, providing clues to the presence of advanced disease
- The enzymes lactate dehydrogenase and creatine kinase are usually normal
- Albumin levels and prothrombin time are normal until late-stage disease
- Iron and ferritin levels may be slightly elevated

Liver biopsy

- Liver biopsy is not necessary for diagnosis but is helpful for grading the severity of disease and staging the degree of fibrosis and permanent architectural damage

Antiviral Therapy for Hepatitis C

Old recommendations

- Combined PEG interferon and Ribavarin

New recommendations

- Preferred regimens in the WHO guidelines – **direct-acting antivirals based on genotype and cirrhosis status**
  - Sofosbuvir, daclatasvir and sofosbuvir/ledipasvir
- Can achieve cure rates above 95%
- Are much more effective, safer and better-tolerated than the older therapies
- WHO is currently updating its treatment guidelines to include pangenotypic

Prevention of Hepatitis C

- Screening of blood, organ, tissue donors
- Household contacts: avoid sharing of shavers, toothbrushes, nail clippers, tweezers
- Education

    - High-risk behavior modification
    - Same risk factors as hepatitis B
- Blood > sex > Perinatal
- HCV vaccine: none available
- HCV immune globulin: none available

Viral Hepatitis D
- Transmission
    - Similar to Hepatitis B
    - No fecal-oral transmission
    - Highest rates in Italy, Venezuela, Africa, Russia, Romania, central Asia and the Middle East
- Co-infection
    - severe acute disease
    - low risk of chronic infection
- Superinfection
    - usually develop chronic HDV infection
    - high risk of severe chronic liver disease
    - may present as an acute hepatitis

Clinical Features
- Coinfection
    - severe acute disease
    - responsive for 50% of fulminant hepatitis
    - low risk of chronic infection (<5%)
- Superinfection
    - usually develop chronic HDV infection (>80%)
    - high risk of severe chronic liver disease
    - may present as an acute hepatitis

Diagnosis of VHD
- Serological test for hepatitis D antibody

Hepatitis D Complications
- 10-15% - develop cirrhosis within two years
- 70% - eventually develop cirrhosis
- 2-20% - fatality rate
- 25-50% - fulminant liver failure in hepatitis B actually due to hepatitis D co-infection

Hepatitis D Prevention
- Hepatitis B vaccine