المحاضرة العاشرة و الثانية عشرة

إلتهاب الكبد الوبائي

- Additional Notes
- Important
- Explanation
- Examples

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تمهيد

- التهاب الكبد الفيروسي هو أحد الأمراض المعدية التي تسببها الفيروسات وتسبب الضرر لخلايا الكبد، قد يكون الضرر الناتج مؤقتاً وقد يكون دائماً. و يتميز التهاب الكبد الفيروسي بوجود خلايا الالتهاب داخل أنسجة الكبد.
- التهاب الكبد مرض تسبّبه عدوى فيروسية في غالب الأحيان. وهناك خمسة فيروسات رئيسية تسبّب ذلك الالتهاب ويُشار إليها بالأنماط A و B و C و D و E. وتثير تلك الأنماط قلقاً كبيراً نظراً لعبء التمريض والوفاة الذي تسبّبه وقدرتها على إحداث فاشيات وأوبئة. ومن الملاحظ، بوجه خاص، أنّ النمطين B و C يؤديان إلى إصابة مئات الملايين من الناس بمرض مزمن ويشكّلان، مجتمعين، أشيع أسباب تشمّع الكبد وسرطان الكبد.
- ويحدث التهابا الكبد A و E، في غالب الأحيان، نتيجة تناول أغذية أو مياه ملوّثة. أمّا التهابات الكبد B و C و D فتحدث، عادة، نتيجة اتصال مع سوائل الجسم الملوّثة عن طريق الحقن. ومن الطرق الشائعة لانتقال تلك الفيروسات تلقي دم ملوّث أو منتجات دموية ملوّثة، والإجراءات الطبية الجائرة التي تستخدم معدات ملوّثة، وفيما يخص التهاب الكبد B انتقال العدوى من الأم إلى طفلها أثناء الولادة، ومن أحد أفراد الأسرة إلى الطفل، وكذلك عن طريق الاتصال الجنسي.
- وقد تحدث عدوى حادة مصحوبة بأعراض محدودة أو بدون أيّة أعراض على الإطلاق، أو قد تنطوي على أعراض مثل اليرقان)اصفرار البشرة والعينين(والبول الداكن والتعب الشديد والغثيان والتقيّؤ والآلام البطنية.

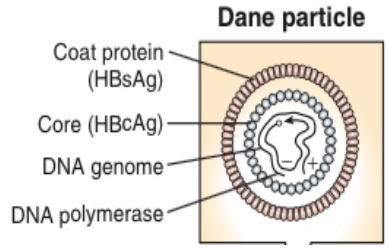
Introduction to viral hepatitis

- Viral hepatitis is an infection of the liver hepatocytes by a virus.
- viral Hepatitis can be

✓ **Primary infection (viruses primarily targeting the liver)**	Transmission	Enterically(fecal- oral route)	H**A**V & H**E**V
		Parenteral (blood-to-blood)	H**B**V, H**C**V, H**D**V & H**G**V
	Genetic material	DNA	H**B**V
		RNA	H**A**V, H**C**V (previously called NON-A NON-B), H**D**V, H**E**V, Hepatitis **G** virus.
✓ **As part of generalized infection**	Herpesviridae ✓ Epstein- Barr virus (EBV) ✓ Cytomegalovirus (CMV) Arboviruses ✓ Yellow Fever virus		

- Chronic hepatitis is limited to hepatitis B, C , D and may be G viruses.
- Just as A and E are at both ends of ABCDE, so they are transmitted by elements of both ends of the GI tract. A = Anal, E = Enteric, **BCD** = **BlooD.**

Hepatitis B Virus (HBV)



Characteristics	Structure	Transmission	Risk of acquiring
✓ Hepadnaviridae family ✓ 8 genotype (A-H), D dominant in Saudi Arabia. ✓ contains the enzyme reverse transcriptase & protease enzyme. ✓ **The serum** of infected individual contains: 1. small spherical free HBsAg particles. 2. Some of HBsAg particles are linked together to form filaments. 3. Dane particles.	1.Outer envelope containing hepatitis B surface antigen (HBsAg). 2. Internal core (nucleocapsid) composed of hepatitis B core antigen (HBcAg). 3. The viral genome which is small partially circular **ds-DNA.** These three together is called Dane particle	▪ **Parentally:** ✓ exposure to infected blood or body fluids. ✓ Contaminated surgical or cosmetics, needles, razors, or tooth brushes. ▪ **Sexually:** The virus is present in blood and body fluids. ▪ **From mother to the fetus** : Mostly: during delivery ,nursing ,breast feeding less likely: through placenta (vertical transmission)	✓ IV drug users ✓ Hemodialysis patients. ✓ Patients receiving clotting factors. ✓ Health care workers ✓ Individuals exposed to risk factors

Hepatitis B Virus (HBV)

- Serological profile of **acute** HBV infection:
  - ✓ 90% of infected adults - Incubation period for 3-4 months → HB-DNA (1st Marker)→ HBsAg (2nd Marker) indicate HB infection **Disappear after LESS THAN 6 MONTHS** → HBeAg (3rd Marker) highly contagious and disappear before HBsAg → Anti-HBc Ab (1st Antibody) persists for years → Anti-HBe appears after HBeAg disappears and persists for weeks to months → Anti-HBs Ab (Last Marker) appears after weeks of HBsAg disappearance and last foe years which indicate HBV immunity → Recover
  - ✓ Less than 9 % of infected adult & 90% of infected infants and 20% of children - HB-DNA OR HBsAg **Last MORE THAN 6 MONTHS → Chronic Hepatitis (**cirrhosis, hepatocellular carcinoma**)**[1]
  - ✓ Less than 1 % - Develop fulminant hepatitis B → death.
- Clinical presentation:
  - ✓ Anicteric phase: Low grade fever, anorexia, malaise, nausea, vomiting and pain at the right upper quadrant of the abdomen, raised liver enzyme
  - ✓ Icteric phase (25%) jaundice ,raised bilirubin leading , dark urine and pale stool
  - ✓ Most acute hepatitis B & C are asymptomatic or anicteric.
  - ✓ majority of patients with chronic hepatitis B and C are asymptomatic or have mild fatigue only

[1] Refer to Pathology lectures

Hepatitis B Virus (HBV)

M "A" as in "acute" fits inside the M of IgM
"C" as in "chronic" fits inside the G of IgG G

Lab diagnosis	vaccine	Prevention & Control:	Treatment
✓ by detection of HBsAg in the blood. ✓ Positive results must be repeated in duplicate. ✓ Repeatedly reactive results must be confirmed by neutralization test. ▪ Additional lab investigations: ✓ Liver function tests (LFT). ✓ Ultrasound of the liver. ✓ Liver biopsy to determine the severity of the diseases. ▪ IgM anti-HBcAg = Acute INFECTION ▪ IgG anti-HBcAg = Chronic INFECTION	genetic engineering in yeast. It is not live attenuated nor killed vaccine ✓ three doses ✓ IM injection at 0 &1 & 6 months ✓ Booster doses may be reacquired after 3-5 years. ✓ It is safe and give excellent protection	▪ Pre-exposure Vaccination ▪ Post-exposure Active Vaccine + Hepatitis B specific immunoglobulin.	limited to patients having chronic hepatitis B based on liver biopsy ✓Pegylated alpha interferon ✓Lamivudine ✓Adefovir

Hepatitis C virus (HCV)

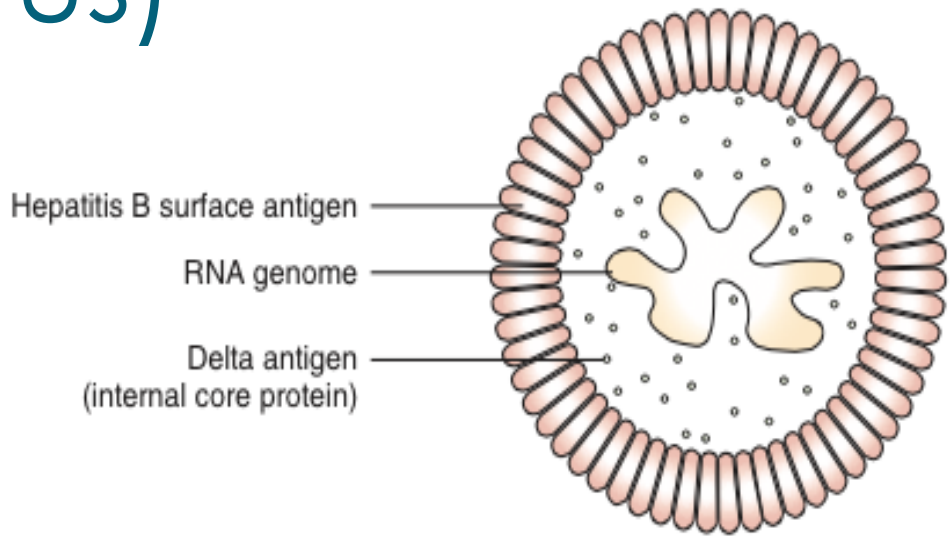
- **Characteristics**
  - ✓ Flaviviridae (Family) hepacivirus (Genus)
  - ✓ 6 major genotypes (1 – 6), genotype 4 is the dominant in Saudi patients.
- **Structure**
  - ✓ outer envelope.
  - ✓ Icosahedral core
  - ✓ ss-RNA gemone.
- **Transmission (similar to HBV)**
  - ✓ Parentally
  - ✓ From mother to child perinatally.
  - ✓ Sexually: rare
- **clinical picture**
  - ✓ Incubation period from 2 to 7 weeks.
  - ✓ Clinically ,the acute infection with HCV is milder than infection with HBV.
  - ✓ Fever ,anorexia, nausea, vomiting , and jaundice are common.
  - ✓ Dark urine ,pale feces , and elevated liver enzyme (transaminase) are seen

Hepatitis C virus (HCV)

- **Lab diagnosis:**
  - ✓ By detection of both:
    - Antibody to HCV in the blood by ELISA, if positive the result must be confirmed by RIBA or PCR.
    - HCV-RNA in the blood using PCR.
- **Hepatitis C markers:**
  - ✓ in 20% of infected individuals Hepatitis C virus RNA (1st Marker of infection) appears after 2-3 weeks of exposure→ hepatitis C core antigen (2nd Marker of infection) appears 3-4 weeks of exposure → IgG Ab to hepatitis C (last marker) appears after 50 days (long window period) **it is not marker of immunity**
  - ✓ 80% will progress to Chronic HC
  - ✓ Less than 1% will develop fulminant hepatitis C → death
- **Treatment**
  - ✓ The currently used treatment is the combined therapy using Pegylated alpha interferon and ribavirin.

Hepatitis D virus (delta virus)

- Composed of small ss-RNA genome, surrounded by delta antigen that form the nucleocapsid.
- It is a defective virus, that cannot replicates by its own. It requires a helper virus. And the helper virus is HBV.
- HBV provides the free HBsAg particles to be used as an envelope.
- Co-infection:
  - ✓ The patient is infected with HBV +HDV at the same time leading to severe acute hepatitis .
  - ✓ Prognosis: recovery is usual.
- Super infection:
  - ✓ In this case, delta virus infects those who are already have chronic hepatitis B leading to severe chronic hepatitis.



Hepatitis G virus

- Hepatitis G is an RNA virus in the *Flavivirus* family, was discovered in 1995.
- Enveloped, ss-RNA with positive polarity.
- It is transmissible by transfusion & parenteral routes.
- Causes mild acute and chronic hepatitis infection.
- Share about 80% sequence homology with HCV.
- Usually occurs as co-infection with HCV, HBV and HIV.

Hepatitis A Virus (HAV)- short incubation hepatitis

- Picornaviridae/ nonenveloped / Icosahedral/ s.s RNA
- Worldwide distribution. Effect children in developing countries
- **Transmission**:
  - ✓ Faecal-oral route [major route]
  - ✓ Sexual contact (homosexual men)
  - ✓ Blood transfusion (v.rarely)
- **Pathogenesis:**

Damage of virus-infected hepatocyte → increase liver enzymes (ALT, AST & Bilirubin)

- **Manifestations**
  - ✓ Pre-icteric phase: fever, fatigue, Vomiting & right upper quadratic pain
  - ✓ Icteric phase: dark urine, pale stool, jaundice
  - ✓ Asymptomatic & anicteric infection which is common
  - ✓ Symptomatic illness increase with age
- **Prognosis**
  - ✓ Self limited disease
  - ✓ Fulminant hepatitis & mortality is rare
  - ✓ No chronicity

Hepatitis A Virus (HAV)

- **Lab diagnosis → serology**
  - ✓ Anti-HAV IgM → new infection
  - ✓ Anti-HAV IgG→ Previous infection & Immunity
- **Treatment**

Supportive therapy

- **Prevention**
  - ✓ Sanitation & hygiene measures
  - ✓ human immunoglobulin
    - Given before or within 2 weeks of exposure to travellers and unvaccinated.
  - ✓ Vaccine
    - inactivated(killed) IM
    - May cause mild local reaction
    - Indicated for people at high risk
    - A combination vaccine HAV + HBV

Hepatitis E Virus (HEV)

- Hepeviridae / s.s RNA
- Outbreak of waterborne & sporadic cases of VH
- Effect young adults
- **Transmission**:
  - ✓ Waterborne
  - ✓ Zoonotic foodborne
  - ✓ Bloodborne
  - ✓ Perinatal
- **Clinical presentation:** will be similar to HAV with the exceptions:
  - ✓ Longer IP =4-8 Weeks
  - ✓ Fulminant disease & Mortality rate is higher than HA
- **Lab diagnosis** → Serology

  ELISA to detect Anti-HE IgM
- **Prevention**
  - ✓ Sanitation & hygiene measures
- No specific treatment or vaccine

Herpesviridae

- dsDNA / Icosahedral / Enveloped Viruses.

A. Epstein Barr Virus EBV

- It is lymphotropic & it has oncogenic properties (e.g. Burkitt's lymphoma & Nasopharyngeal carcinoma)
- **Distribution**: worldwide
- **Transmission**: **Saliva**
- **Age** based on the socio-economic status if it is
  - ✓ Low class → early childhood
  - ✓ High class → adolescence
- **Diagnosis**
  - ✓ Hematology
    - Increase WBC, Lymphocytosis
  - ✓ Serology
    - Non-specific AB test : Heterophile Abs positive, Paul-Bunnell or mono-spot test
    - specific AB test: IgM Abs to EBV capsid antigen

- **Clinical Features:**

  1.Immunocompetent host

  - Asymptomatic
  - Infectious mononucleosis [glandular fever]
    - ✓Mainly in teenagers & young adults
    - ✓Incubation period = 4-7 weeks
    - ✓Fever, pharyngitis, malaise, LAP, hepatosplenomegaly & abnormal LFT with or without hepatitis .
    - ✓Complications rare but sever
  - Chronic EBV infection (when last more than 6 months symptoms

  2.Immunocompromised host

  - Lymphoproliferative disease (LD)

- **Treatment:**

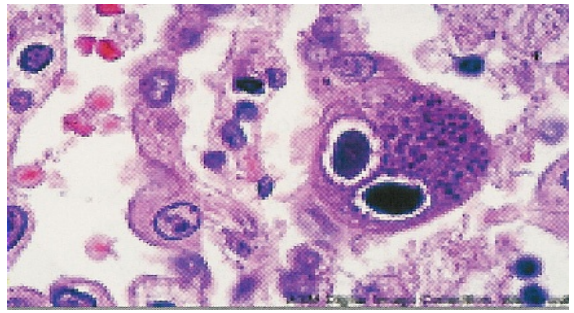
  Antiviral drug is not effective in IMN

- **Prevention:**

  No vaccine

B. Cytomegalovirus (CMV)

- Infected cell enlarged with multinucleated.
- **Distribution**: worldwide.
- **Transmission:**
  - Early in life: Transplacental / Birth canal / Breast milk.
  - Young children: saliva.
  - Later in life: sexual contact / Blood transfusion / organ transplant.
- **Diagnosis;**
  - Histology: Intranuclear inclusion bodies [Owl's – eye]
  - Culture:
    - ✓ In human fibroblast
    - ✓ 1-4 wks Cytopathic effect
    - ✓ Shell Vial Assay 1-3 days
  - Serology:
    - ✓ Antibodies : IgM : current infection / IgG: previous exposure
    - ✓ Antigen: CMV pp65 Ag by IFA
  - PCR



Owl's – eye

- **Clinical Features:**
  - Acquired Infections:
    A. Immunocompetent host
       - ✓ Asymptomatic
       - ✓ Self limited illness : Hepatitis, Infectious mononucleosis like syndrome (Heterophile AB is negative)

    B. Immunocompromised host: Encephalitis, Retinitis, pneumonia, Hepatitis, Colitis
  - Congenital Infections
- **Treatment:**
  - ✓ Ganciclovir→ is effective in the Rx of severe CMV inf.
  - ✓ Foscarnet → the 2nd drug of choice .
- **Prevention:**
  - ✓ Screening (Organ donors, Organ recipients, Blood donors)
  - ✓ Leukocyte-depleted blood .
  - ✓ Prophylaxis: Ganciclovir , CMVIG (CMV Immunoglobulin).
  - ✓ No vaccine.

Arthropod –borne Viruses (Arboviruses)

Yellow Fever virus (YFV)

- Flaviviridae / s.s RNA
- Asymptomatic to Jaundice, Fever, hemorrhage, renal failure.
- **Epidemiology**: Tropical Africa & South America.
- **Diagnosis:**
  - ✓ Isolation
  - ✓ IgM -AB* - ELISA, IF: (most used)
  - ✓ YFV- RNA by RT-PCR
- **Prevention:**
  1. Vector Control: Elimination of vector breading sites / using insecticides /Avoidance contact with vectors
  2. Vaccines : Yellow Fever vaccine (Life attenuated vaccine, one dose /10 years)

Types	Vector	Reservoir	Accidental host	Disease of:
Jungle Yellow Fever	Mosquito	Monkey	Humans	Monkeys
Urban Yellow Fever		Human	---	Humans