٠٥/٠٢/١٤٤١

Approach to pediatric hepatology

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Hepatitis A

* RNA virus
* Incubation period 15-19 days
* Transmission → fecal-oral route
* Most common presentation → flu-like symptoms

- acute and benign hepatitis.
- Fulminant hepatic failure....very..rare..(1%..of cases)
- a member of the picornavirus family.

سبب المشكلة إنه the prevalance of Hep A is very large making that 1% significant.

* The most common cause for acute liver transplant in adults is due to Hepatitis A (paracetamol بعد ال)

* we don't have chronic hepatitis A
* There is no carrier

* بتيجي ال presentation jaundice
* و كل ما كان ال pt أكبر (adult) بتعبر أكثر chances to present as jaundice و ال complications أكثر

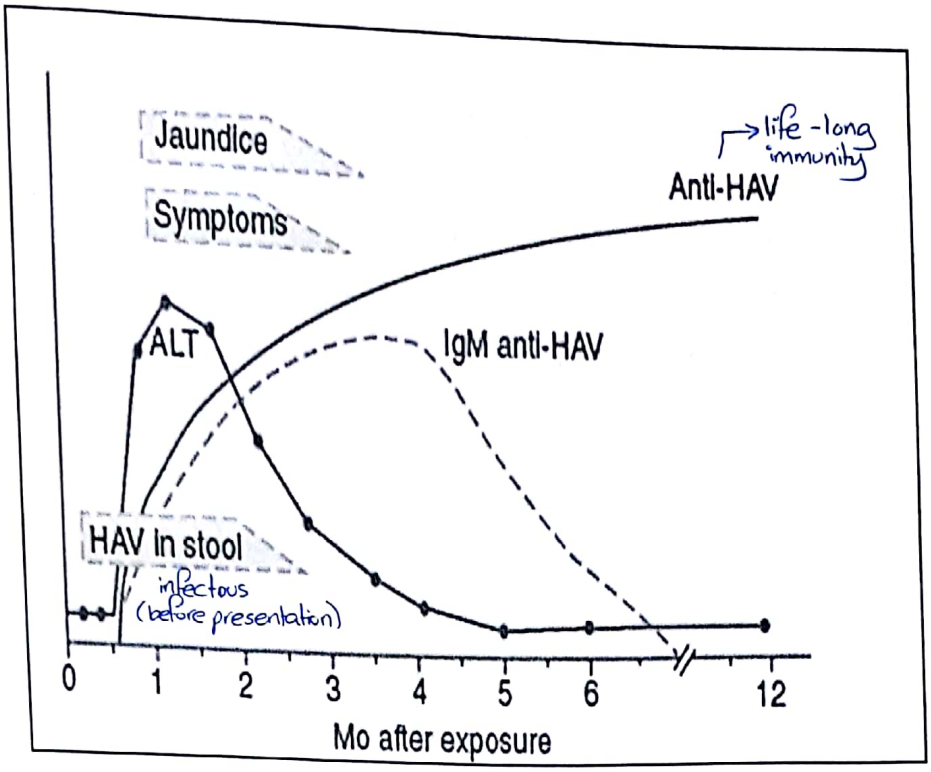
Hepatitis A

- Transmission is almost always by person-to-person contact
- The incubation period for HAV is ~3 wk.
- Fecal excretion of the virus

* Infectous period (when is a person infectous): 1-2 weeks before the onset of the illness

Hepatitis A

- Clinical symptoms gastro-enteritis or flu-like symptoms (vague presentation)
- The illness is much more likely to be symptomatic with jaundice in...older pts. (adolescents) and immunocompramised pts



Hepatitis A

- Diagnosis → by looking for IgM anti-HAV (this antibody can remain +ve for 6 months, but when you have a pt with jaundice and a +ve IgM, this is hep A until proven otherwise)
- Types of antibodies present
  IgM and IgG

Hepatitis A

- Prognosis → very good prognosis (unless in the 1% cases of fulminant liver failure)
- Complications
  - ↳ acute liver failure

→ When do we give pts w/ Hep A immunoglobulins?
- Immunocompramised pts
- أو إذا واحد ساكن عند endemic area بفترة ما بتسمحلي أعطيه الـ vaccine
(يعني مثلاً إذا راح يسافر خلال # أسبوع (المطعوم بحتاج ٢ أسابيع ليشتغل) ، فزاد منعطيه immunoglobulins و المطعوم ، حتى نحميه الـ immunoglobulins لحد ما يشتغل الـ vaccine)

Hepatitis A

- Management
  - Medical
    - Supportive (IV fluids)
    - immunoglobulin
  - Indications for admission
    - If coagulopathy is present
    - vomitting and ↓ oral intake
    - If pt has hepatic encephalopathy
  - Liver transplant

* هدول اللي حكينلكم الدكتورة *

خارجي * From medscape : Admit pts w/ hepatitis if they are showing any S&S suggestive of severe complications :
- Hepatic encephalopathy (altered mental status, agitation, behavior or personality changes, changes in their sleep-wake cycle)
- PT longer than 3 sec.
- Bilirubin level >30 mg/dl
- Intractable vomitting
- Hypoglycemia
- significant electrolyte or fluid disturbances
- significant cormorbid illness (ex. pt above 50 yrs old, or immunocompramised)

Hepatitis A

- Prevention
  - Hygien
  - Vaccine
    - When do we give the vaccine?

(2 dose vaccine) - After the age of 1 year
and b/w the first and second dose 6 months

→ Who is the most important person to give Hep A vaccine?
Any child with a chronic liver disease must be given Hep A vaccine (ex. if child has hep B or C, Allagile syndrome, wilson's disease)

* Hep A vaccine is very good, it has a seroconversion of 90% in the first dose and 95% in the 2nd dose

CHRONIC LIVER DISEASES

↳ > 6 months

٠٥/٠٢/١٤٤١

History and physical signs of chronic liver disease

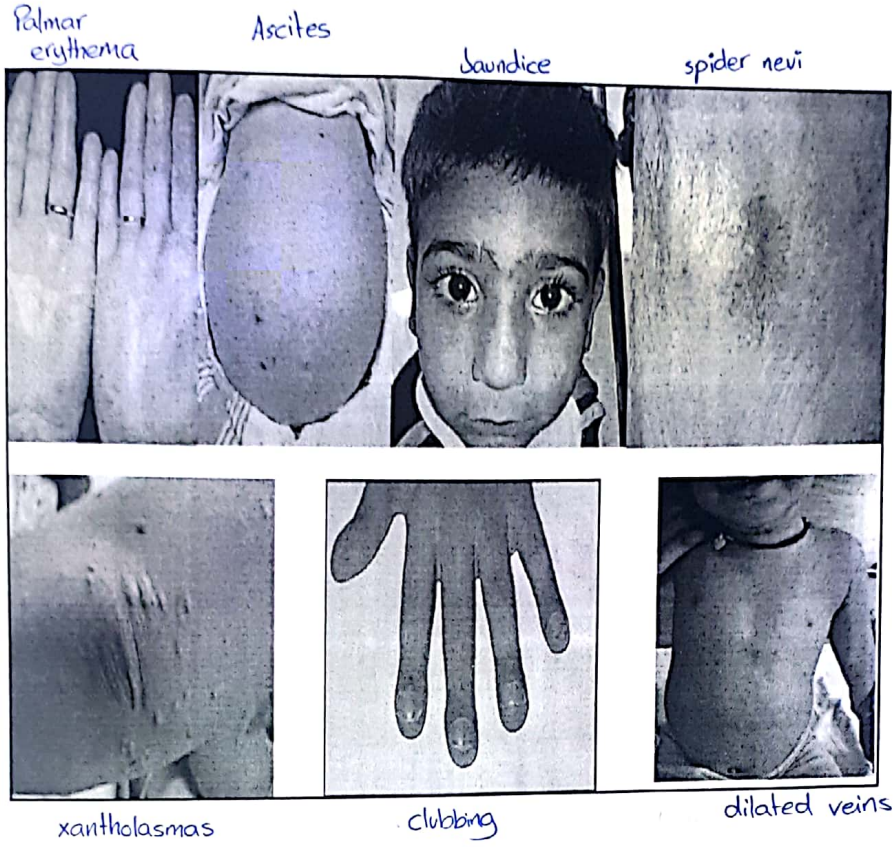
- Family history of liver disease or liver transplantation → for inherited causes (ex. wilson's disease)
- History to suggest viral hepatitis → - recent travel
  - contact w/ sick ppl
  - blood transfussion (زمان) ← لما كانوا يعملوا screening
  - tattoos
  - drug abuse
  - pts on dialysis
  - contact w/ pts w/ hepatitis
- Consanguinity for inherited disorders

History and physical signs of chronic liver disease

- Non-specific fatigue, headache, GI manifestations, fever, abd. pain
- Failure to thrive → it's a chronic disease, and if there is an element of cholestasis → malabsorption
- Pruritus → due to the deposition of conjugated bilirubin in the skin
- Jaundice
- pallor → anemia of chronic disease / also hep B can have manifestations on the bone marrow / hemolysis in wilson's disease (due to presence of copper in the blood stream)
- clubbing ← due to presence of toxins causing constriction of the vasculature in the peripheral part of the body
- Symptoms of portal hypertension → Abdominal distention, Hepatosplenomegaly, Caput medusa, Ascites, Hematomesis due to upper GI bleeding from varices (esophageal), Parotid enlargement, Spider nevi, Gynecomastia, Hypogondism
- Hepatomegaly (early) vs shrunken liver (cirrhosis)
- Neurological signes ↳ from hepatic encephalopathy

*Presence of a hemolytic episode in a child with elevated liver enzymes and cholestasis is wilson's disease until proven otherwise

Palmar eryth



Complications of chronic liver disease

hepatic encephalopathy أهم وحدة

Complications of chronic liver disease

- Hepatic encephalopathy

4 stages

	STAGES I	II	III	IV → needs liver trasplant
Symptoms	Periods of lethargy, euphoria; reversal of day-night sleeping; may be alert	Drowsiness, inappropriate behavior, agitation, wide mood swings, disorientation	Stupor but arousable, confused, incoherent speech	Coma IVa responds to noxious stimuli IVb no response
Signs	Trouble drawing figures, performing mental tasks تجيه شارد	Asterixis, fetor hepaticus, incontinence	Asterixis, hyperreflexia, extensor reflexes, rigidity	Areflexia, no asterixis, flaccidity
Electroencephalogram EEG	Normal	Generalized slowing, q waves	Markedly abnormal, triphasic waves	Markedly abnormal bilateral slowing, d waves, electric-cortical silence

أي طفل chronic liver disease لازم نشوف الـ reflexes

Complications of chronic liver disease

- Cirrhosis
- Hepatorenal syndrome → indication for liver transplant → presents w/ oligouria and ↑ creatinine
- Hepatopulmonary syndrome → 1st presentation → hypoxia (↓ O_2 sat) → indication for liver transplant
- Hepatocellular carcinoma

(Hepatorenal & hepatopulmonary syndromes) → due to vasoconstriction

ما في رجعة

CHRONIC VIRAL HEPATITIS

FEATURES OF THE HEPATOTROPIC VIRUSES

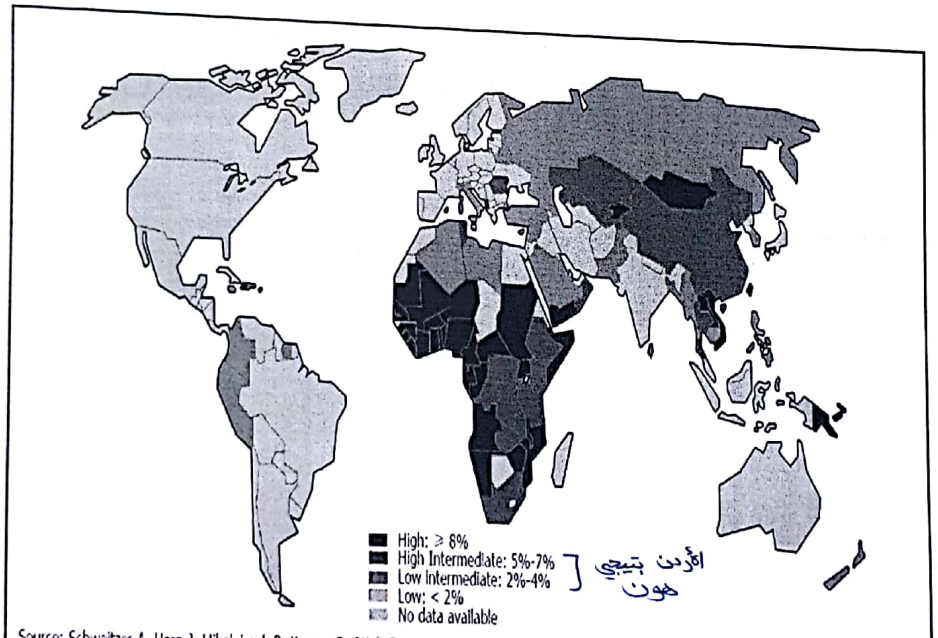
VIROLOGY	HAV RNA	HBV DNA	HCV RNA	HDV RNA	HEV RNA
Incubation (days)	15-19	60-180	14-160	21-42	21-63
Transmission					
• Parenteral	Rare	Yes	Yes	Yes	No
• Fecal-oral	Yes	No	No	No	Yes
• Sexual	No	Yes	Yes	Yes	No
• Perinatal	No	Yes	Rare	Yes	No
Chronic infection	No	Yes	Yes	Yes	No
Fulminant disease	Rare	Yes	Rare	Yes	Yes

Hepatitis B Virus

- DNA virus
- Can cause chronic Hep B
- Has a vaccine (effective)
- ↑ risk for cancer
- The younger the age of infx the more complications

HBV DNA has four long open reading frames:

- S gene & pre-S region encodes for surface Ag (HBsAg)
- C gene encodes for viral nucleocapsid Ag (core) & HBeAg (envelope)
- P gene encodes DNA polymerase
- X gene has enhancer promoter complex to direct transcription of host gene



Source: Schweitzer A, Horn J, Mikolajczyk R, Krause G, Ott J. Estimations of worldwide prevalence of chronic heptitis B virus infection: a systematic review of data published between 1965 and 2013. The Lancet. 2015 Jul 28; 386(10003): 1546-1555.

Hepatitis B prevalence

Clinical presentation of HBV

- Acute hepatitis → in 30% of cases
- Chronic > 6 mths
- extrahepatic immune mediated
  - ↳ renal membranoproliferative disorders
  - ↳ Gullien Barre syndrome
  - ↳ Polymyalgia rheumatica
  - ↳ Vasculitis (polyarteritis nodosa)

Risk factors for HBV infection

- Intravenous drugs or blood products
- Acupuncture or tattoos
- Sexual contact
- Institutional care, and intimate contact with carriers.
- Occupational exposure (health care workers)
- * Perinatal exposure to HBsAg positive mother
- No risk factors are identified in ~40% of cases.

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Transmission of Hep B → vertical (mother to child)
→ Horizontal

اللي بحكمنا بالطفل أول ما يولد انه يكون لسا عنده antibodies من الأم عشان يكون فما بستفيد من إنه اشوف ال antibodies # تبعه الا بعد ٦ أشهر لسنة فية المناعة منه مش من الام

بس عادة لما تكون الأم عندها HbsAg +ve و عندها high viral load و HbeAg +ve
She is very likely to transmit the infx to the baby.

فاحنا أول ما يولد البيبي معطيه Immunoglobulins و معطيه ال vaccine (at different sites) ك مثلاً بنعطيه المطعوم عالرجل اليمين و ال imunoglobulins عالشمال. (عشان ما يلغوا بعض)

و بعدين منعيد المطعوم بعد شهر و بعدين بعد شهرين

و إذا كان البيبي preterm و أقل من ٢،٥ كيلو بوخذ ٤ جرع من المطعوم

Perinatal transmission of HBV

- In children, the most important risk factor for acquisition of HBV is perinatal exposure to an HBsAg-positive mother
- Serologic markers of infection and antigenemia appear 1-3 mo after birth, suggesting that transmission occurred at the time of delivery.
- Up to 90% of these infants are asymptomatic but become chronically infected.

*Usually transmisson occurs during delivery (not during pregnancy)

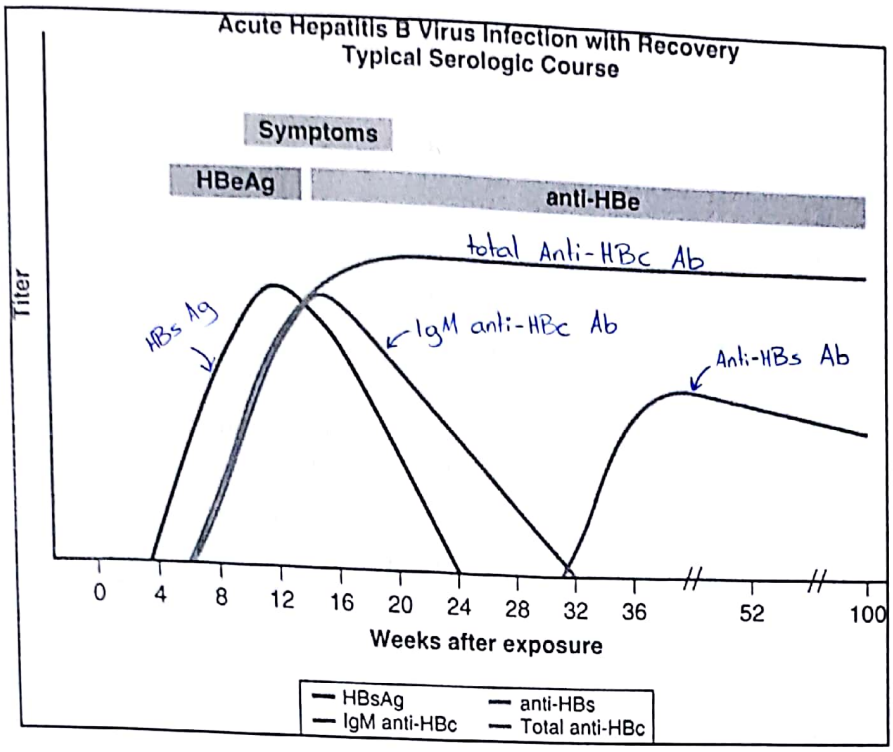
*في نسبة قليلة جداً من الأطفال لاحظوا انه إذا عملولهم Hep B DNA by PCR بتطلع +ve على عمر ٣ أشهر ، و هاد الإشي suggests that the infx occurred during pregnancy ← و هدول بالذات ما بنربط معهم لا المطعوم و لا immunoglobulins

Serology of HBV

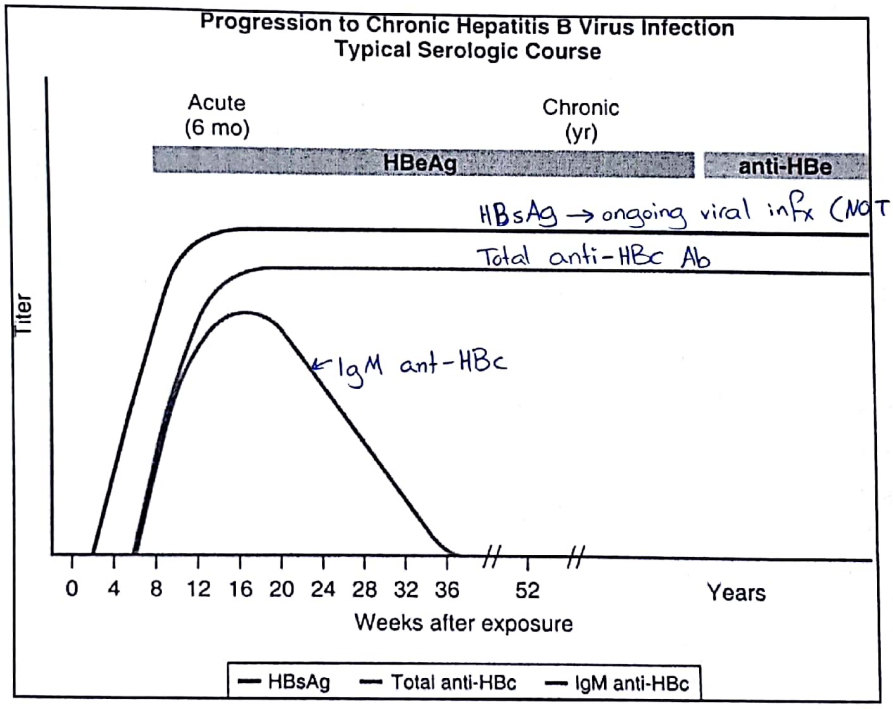
*لما نحكي core يعني المشكلة سيرها a real virus / أما لما يكون ال core -ve معناته vaccination

منفرق فرق بين ✗ immunity due to vaccination and immunity due to infx by Heb B
→ vaccination core -ve / surface +ve
→ Infection core +ve / surface +ve

- Acute hepatitis: HBsAg < 6 months, HBcAb IgM
- HBeAg: correlate with high infectivity and viral replication
  HBe Ag +ve has higher rate of transmission than HBeAg -ve
  (HBeAg +ve ← الام اللي بنعطي الانتي antiviral meds و هي حامل)
- HBcAb IgG remains positive after the infection regardless the outcome (resolved or carrier or chronic phase)
  ال core بس يدلني انه صار في وجود of a real live virus in the system
- Chronic HBV= persistence of HBsAg > 6 months



All antigens are -ve



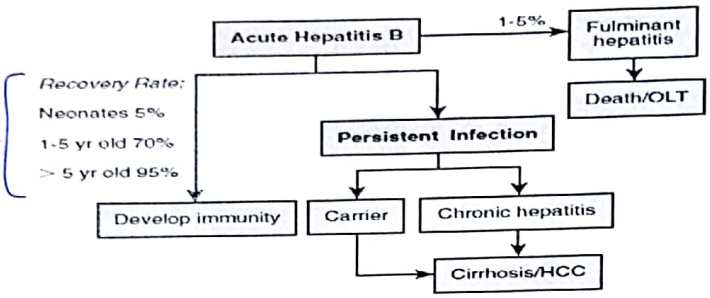
Serology of HBV

- Positive HBsAb only...Immunization by vaccine
- Positive HBsAb &HBcAb IgG..Immunization from Heb B viral infx
- Positive HBsAg >6 mo & normal liver enzymes and negative HBV DNA & negative HBeAg.....Carrier state (Chronic) ~~(immunotolerant)~~
- Positive HBsAg >6 mo & elevated liver enzymes and positive HBV DNA and +/- HBeAg.....Chronic..active hep
- ~~liver enzymes and positive HBV DNA and +/- HBeAg..~~
- liver enzymes normal and DNA +ve → immunotolerant

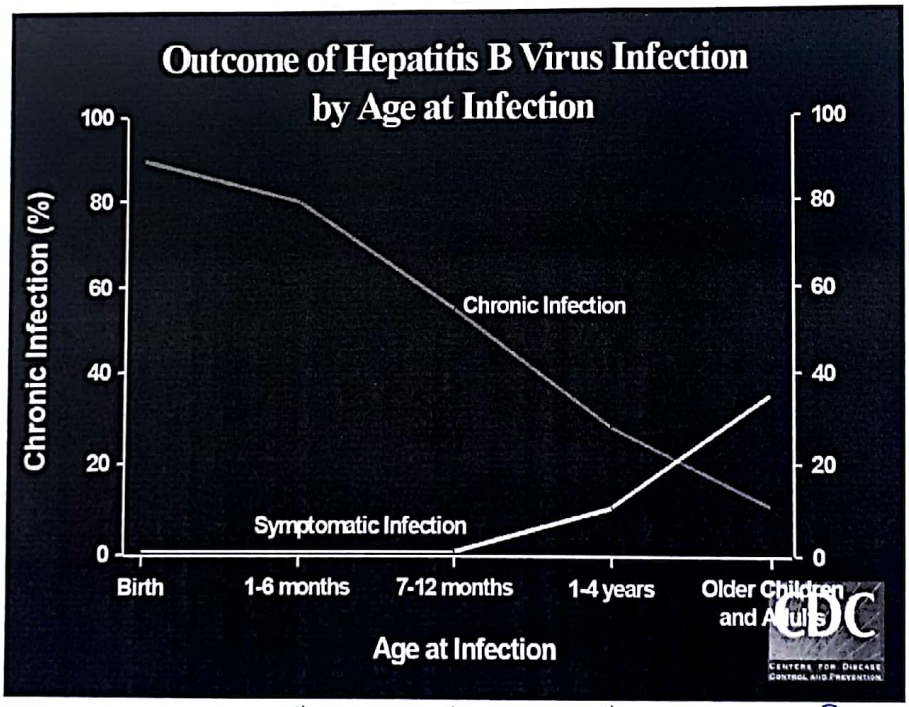
Hepatitis B transmission

- The hepatitis B virus cannot penetrate unbroken skin and is killed by the digestive juices in the stomach if it is swallowed.
- There is a 95% chance that a mother with chronic hepatitis B will pass it on to her baby
- If a mother with hepatitis B passes on the virus to her baby at birth there is a 90% chance that the baby will go on to develop chronic (long term) hepatitis B.
- Babies born to hepatitis B positive mothers can be given vaccination and hepatitis B immunoglobulin at birth, which reduces the risk of hepatitis B transmission to only 5%
- Overall the risk of acquiring hepatitis B from needle-stick (or sharps) injury in a health care setting is around 30%.

Natural course in Acute hepatitis B



كلما ↑ زاد العمر ← recovery rate زاد الـ



The younger the age, the higher the chances of chronicity.

Management of HBV

- Prevention → by vaccination and education and management of a baby w/ HBsAg +ve
- Prophylaxis → Immunoglobulins and vaccination
- Therapy
  - ↳ usually in children we don't give therapy we give therapy in the case of an active hep B (elevated liver enzymes)

2x the normal يكون ارتفاع elevation لل و ↵ for 6 months

antiviral meds. يعطى و interferons يعطى *

Prevention of Hepatitis B Infection

- **Hepatitis B vaccine**
  - Recombinant DNA vaccine
  - HBsAg
  - 3 doses (0, 1 month, 6-12 months) ← طفل المواعيد لطفل امه HBsAg +ve
  - Preterm

Prevention of Hepatitis B Infection

- **Hepatitis B- specific immunoglobulin**
  - Indications:
    - Contaminated needle-stick exposure
    - Perinatal exposure for newborns of positive HBsAg mothers within 12 hours after birth (in addition to first doe of HBV vaccine)
    - Pre and post liver transplant for HBsAg patient

Treatment of HBV

- **Acute infection** (30% of pts)
  - supportive
  - Careful monitoring for encephalopathy and acute liver failure

بالنسبة اللي بتحولوا فيرا ل chronic بعطيهم
antiviral medications و ال interferons ال

Treatment of HBV

- Treatment is only indicated for patients in the immune-active
- Goals of Rx
  - converting to carrier state → get liver enzymes normal and Hep B DNA -ve
  - Eliminate the virus
  - Prevent progression to cirrhosis &/or HCC

Treatment of HBV

- **Indications for therapy**
  - HBsAg positive for >6 mo
  - Evidence of ongoing viral replication (presence of HBeAg & HBV- DNA for at least 6 months).
  - ALT> twice upper limit of normal
  - Evidence chronic active hepatitis on liver biopsy.

HEPATITIS C VIRUS

Hepatitis C Virus

- RNA virus
- 6 genotypes → prognosis for each genotype is different
- 85% of infected cases remained chronic

↳ so we need to know the genotypes in order to give the medications

cure حالياً صار في أوروبا و بمصر بس بيعتمد على ال genotype

FEATURES OF THE HEPATOTROPIC VIRUSES

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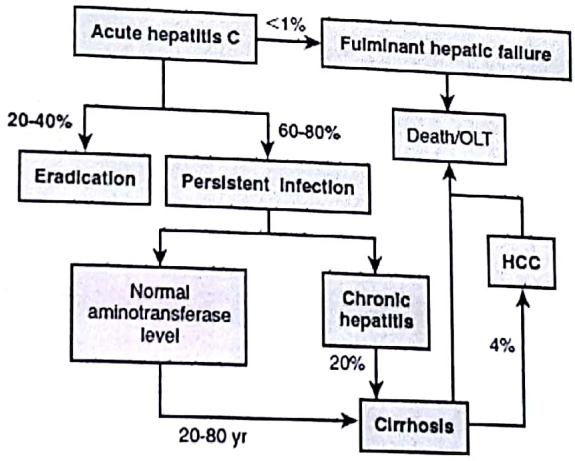
Chronic infection	No	Yes	Yes	Yes	No
Fulminant disease	Rare	Yes	Rare	Yes	Yes

Natural history of HCV infection



85-95% يجيب عندهم cirrhosis

ما الربا علاقة بالعمر (Hep B ممكن ذي

Risk factors for HCV transmission

- blood transfusion
- Illegal drug use
- exposure to blood or blood products
- Sexual transmission
- Occupational exposure
- 10% of new infections has no known transmission source.

بس الـ transmission mother-child لهيك ما في حدا بقدر يحكيلك
بصير في transmission ٪١٠٠ لأنه نادر
مع إنه في أطفال عندهم Hep C ~~[illegible]~~
بس بيجوا على عمر ٣ أو ٤ سنين فصعب
تحدد إنه هو من امّه أثناء الحمل أو الولادة
ولا إجاهم بعدين

Diagnosis of HCV infection

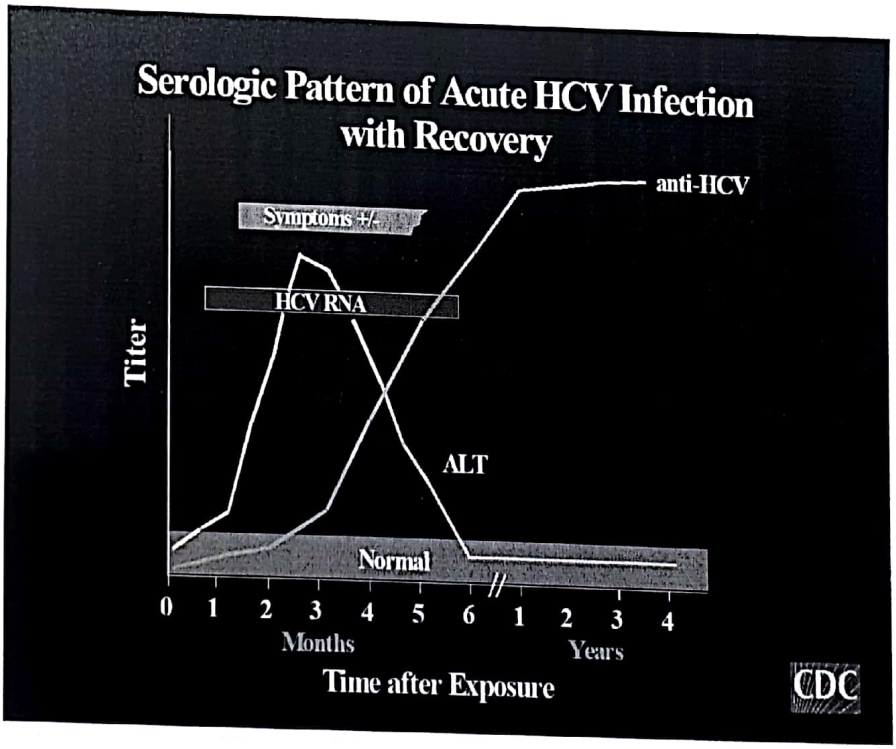
- HCV antibodies → ما بفيدني
- HCV by PCR

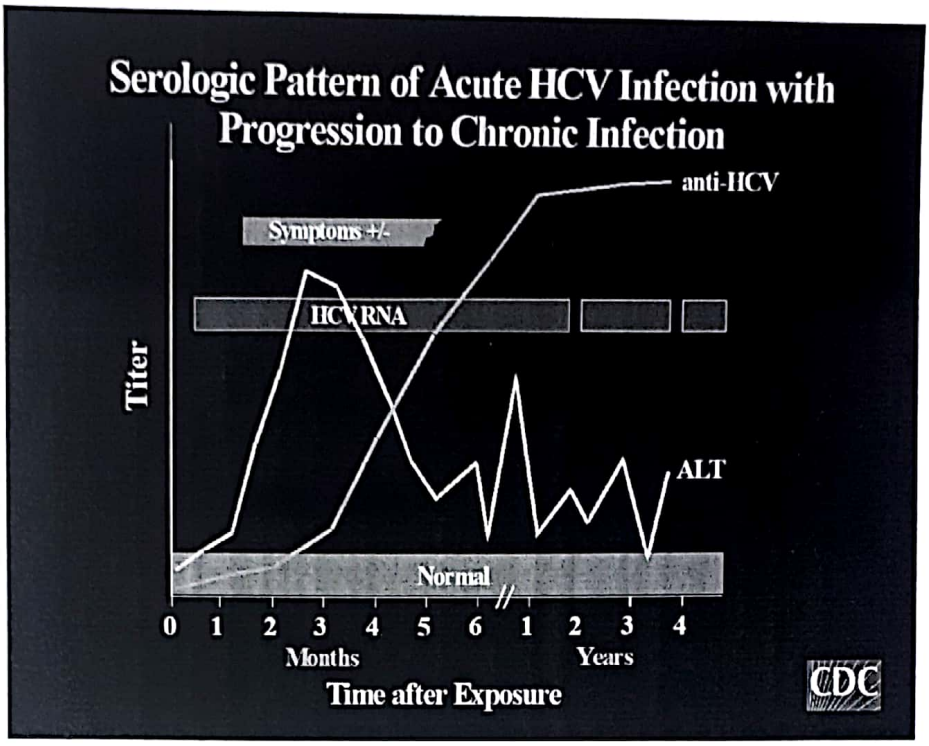
whenever we have infx for لأنه hep C we will have Abs
chronic و recovery و acute بغض النظر كان
But whenever we have HCV PCR +ve → we have an ongoing infx

Serology of HCV

- Positive HCV antibodies → exposed
- Acute infection PCR +ve
- Chronic infection PCR +ve > 6 mths
- Resolved infection → Ab +ve and PCR (RNA) -ve

  ALT and AST normal





Prevention of Hepatitis C Virus Infection

- No protective immunoglobulin
- No vaccine available
- Precautions , behavioral modifications
- Prevention by screening donated blood

Treatment of Hepatitis C virus

Indications for treatment:

- Detectable HCV- RNA by PCR > 6 mo
- Elevated ALT (hit on the liver)
- Evidence of chronic hepatitis and fibrosis by liver biopsy

↳ because it may be curable depending on the genotype

NON-VIRAL CHRONIC HEPATITIS

WILSON DISEASE
(HEPATOLENTICULAR DEGENERATION)

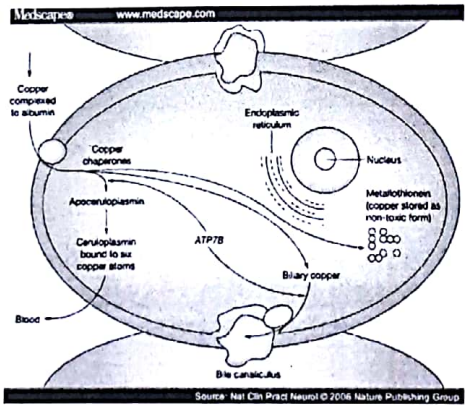
→ Age of presentation → 3 yrs old

المشكلة بالـ copper ← بيجي لها absorption من الـ small intestine بتروح على الـ liver و ما بتطلع منها ← بتعمل destruction للكبد و بتيجي في الـ free copper in the blood و بتعمل hemolysis و بتيجي deposition بأعضاء تانية زي العين و الـ basal ganglia و القلب (... hypo or hyperthyroidism/ DM) endocrinopathies بتعمل endocrine على و

↳ cardiomyopathy

*Note
neurological manifestations usually appear in adulthood.

Wilson's disease pathophysiology



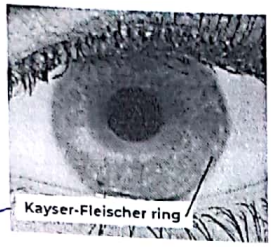
✗ Dx → Ceruloplasmin low

24 hr collection for urinary copper is ↑
↳ if -ve we do chelation

*Normal ceruloplasmin does not rule out Wilson's, remember that it's an acute phase reactant

Gold standard: Biopsy with dry weight copper level

Wilson's disease Clinical manifestations



using a slit lamp we can see it via the naked eye if it was severe

خاصة بالعيون العلونة

* One of the causes of RTA is wilson's disease

Wilson disease

Diagnosis

- low serum ceruloplasmin
- Elevated serum copper
- High 24 hr urine copper
- Quantitative copper in liver biopsy is the definitive diagnostic test

Management of Wilson disease

- Compensated liver disease
- decompensated cirrhosis or fulminant liver failure → liver transplant
- Screen the siblings with ceruloplasmin or genetic mutation if it is known from proband case

- We give Zinc (because it ↓ copper absorption from the small intestine)
and chelating agents

-what foods contain copper ?
everything basically
especially pepsi , chocolate (especially dark)

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis (AIH)

- Autoimmune hepatitis is... inflammation of the liver due to the presence of autoantibodies
  - elevated serum aminotransaminase concentrations, (AST and ALT elevated)
  - liver-associated serum autoantibodies, (anti-smooth ms. / anti-liver-kidney / anti-mitochodrial)
  - +/- hypergammaglobulinemia.
- Might be associated with other autoimmune diseases

Autoimmune hepatitis (AIH)

Clinical picture

↳ elevation for 6 months, we should look for autoantibodies

- Asymptomatic elevation of liver enzymes
- Non-specific
- Jaundice
- Amenorrhea
- Stigmata of chronic liver disease
- extrahepatic manifestations
- features of cirrhosis

↳ other autoimmune diseases

2 types

Table 354-2 CLASSIFICATION OF AUTOIMMUNE HEPATITIS

VARIABLE	TYPE 1 AUTOIMMUNE HEPATITIS	TYPE 2 AUTOIMMUNE HEPATITIS
Characteristic autoantibodies	Antinuclear antibody*	Antibody against liver-kidney microsome 1*
	Smooth-muscle antibody*	
	Antiactin antibody†	Antibody against liver cytosol 1*
	Autoantibodies against soluble liver antigen and liver-pancreas antigen†	
	Atypical perinuclear antineutrophil cytoplasmic antibody	
Geographic variation	Worldwide	Worldwide; rare in North America
Age at presentation	Any age	Predominantly childhood and young adulthood
Sex of patients	Female in ~75% of cases	Female in ~95% of cases
Association with other autoimmune diseases	Common	Common‡
Clinical severity	Broad range	Generally severe
Histopathologic features at presentation	Broad range	Generally advanced
Treatment failure	Infrequent	Frequent
Relapse after drug withdrawal	Variable	Common
Need for long-term maintenance	Variable	~100%

→ complicated
transplant و إذا عملت
لكبد جديد . بعود . يرجع
* mainly in females
* mainly in childhood
* Almost always associated w/ another autoimmune disease

* In type one → we can stop the medication at some point but in type 2 we can NOT

Diagnosis of AIH

- Elevation of transaminases
- Elevated gamma-globulin levels
- The presence of autoantibodies
- Characteristic histologic findings
  - * ↳ -Plasma cell infiltrate
  - - Bridging fibrosis between portal triads

Treatment of AIH

by Immunosuppression

- Prednisone (steroids)
- Azathioprine or 6-mercaptopurine
- Liver transplantation for patients with end-stage liver disease
- Disease can recur after liver transplantation (especially in type 2)

Homework

Dig up

- How do we screen blood for hepatitis b ?
- What medications are used to treatment of hepatitis B?
- What medications are used to treatment of hepatitis c?
- How to follow up patients with hepatitis C?