Subject: Hyper Bilirubinemia — Dr. Salma

* Its Mainly about cholestasis (Direct hyperbilirubinemia)
↳ indirect HyperB is explained in Afternoon session.

* Hyperbilirubinemia is elevated Bilirubin (B) levels in the blood leading to yellowish discoloration of skin & sclera.

* Types of hyperB → 1- Direct (conjugated)
2- unconjugated (indirect)

↳ Depends on the mechanism.

* Treatment of hyperB (indirect) is by phototherapy
→ it causes isomerization of the indirect B and make it into water soluble substance than can be excreted.

* For Diagnosis & monitoring of B levels, new studies suggest testing the CO levels in the breath, since Biliverdin and CO are produced in equimolar amounts → This allows us to see the level of B instead of taking blood samples from the baby multiple times → But the study isn't confirmed yet!.

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* Inherited Disorders of B conjugation *

① Crigler - Najjar Syndrome.

↳ Autosomal Recessive Disorder

↳ There's no hemolysis, or sepsis, or UTI, it's just a problem in the conjugation of B → indirect hyperB

* Has 2 types → ① Type I → More severe
↳ complete absence of UDP-glucorenyl transferase enzyme which is responsible for conjugation

② Type II → less severe
↳ partial absence of the enzyme

* How to differentiate bet. them ?
↳ we give phenobarbital (Luminal) → this will accelerate conjugation ⇒ If there's response → you are dealing w/ type II

⇒ If no response → Type I

* Type I is more severe, presents earlier than type II & can present w/ severe fatal manifestations before Type II

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* Hyper B pts have clay colored stool

* Crigler Najar Synd don't present w/ anemia bcause there's no hemolysis

* pts are treated w/ photo therapy (all night when they sleep)

* If B levels got very high → we do exchange transfusion or plasmapharesis (easier)

~~② Gilbert Syndrome~~
~~↳ very low incidence~~

② Gilbert syndrome

↳ indirect hyper B (mild)
- presents at adult hood, not seen in pediatric
- present w/ jaundiced sclera when pt is sick or has flue symptoms, other than that no symptoms.

- Have Normal liver enzymes, a little elevated B.
- doesn't need treatment and doesn't lead to any complication

Cholestasis

↳ Its Direct hyperB due to abstruction (↓efflux of B from the liver, at the level of hepatocytes)
↳ any pathology in the biliary tract, or hepatocytes.. CBD, Gallbladder, ampulla of vater ⟶ will lead to cholestasis

* Cholestasis ⇒ ~~If total B ⟶ 5mg/dl~~
- If direct B > 2 mg/dl
or - If direct B was > 20% of the total B

(e.g → total B was 5 mg/dl, Direct B should be ≥1 (>20% of total B).

(e.g → total B = 100 mg/dl, Direct B = 50 mg/dl ⇒ cholestasis).

* In cholestasis, if PT or INR were Low or Normal ⇒ This means that we don't have liver failure.

* Indicators of liver function :-
① PT / INR → for acute Liver failure, because their half life is hours or minutes

② albumin → Its decreases after 21 days (half life) so its not for acute liver failure.

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* Direct hyper B is always pathological → you need to find the cause

↳ But indirect hyper B could be physeological Jaundice

* Allagile Syndrome or C.F → Problem is at the level of bile ductules

* Choledochal cyst → at level of intrahepatic billiary tree to CBD.

↳ present at different age.

has different sizes → small cyst present at 3-4 years old + Jaundice.

→ But large cyst can present at Birth.

* Gallstones → in cystic, common bile duct

* Billiary atrasia → within hepatic duct, could involve all the Billiary tree.

* other causes of cholestasis :-

1- Hypo Hyroidism

2- Tyrosinemia

3- Galactosemia

4- Cholangitis

5- pancreatic Tumors (not in babies)

6- annular pancreas

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4- Cystic fibrosis

8- Inspissated Bile Syndrome (due to ceftriaxone Abx)
↳ Due to obstruction of extrahepatic bile system

* History *

1- Clay colored stool → most common cause is Billiary atrasia (BA)

2- Tea colored urine → cholestasis

3- Excessive bleeding → due to coagulopathy

[baby w/ hepatosplenomegaly, very high PT / INR, excessive bleeding, Jaundice, sick child, 1m old
⇒ TORCH,
Tyrosinemia *عدوى*]

4- vomiting → - Billiary vomiting → obstruction below ampulla of vater
- Non Billious → pyloric stenosis

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5- Breast feeding vs Lactose free formula ?
formular

↳ If there's family hx of Galactosemia & his mom decided to give the new baby lactose free formula → No symptoms will appear

↳ so ask for the formula.

6- Prenatal US → can show choledocal cyst.

7- weight gain → If baby isn't gaining weight → think metabolic problems or inborn errors of metabolism.

*physical Examination *

1- General look of pt → If ill think about sth acute → sepsis or inborn error of Metabolism.

2- Facial features → Allagile Syndrome, Zellweger Syndrome → have very distinct facial features

3- Growth parameters → If Good → Billiary Atrasia
If abnormal → Metabolic

* If 4 years old baby, chelestasis & failure to thrive what's the case ? → CF

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4- Fundascopy → look for Bilateral cataract

*) If a baby w/ Jaundice, cholestasis, cataract, hepatosplenomegaly ⇨ Its Galactosemia

5- Abdominal exam → check for hepatosplenomegaly, Chronic liver disease

*Stigmata of chronic liver Disease :-

1- Ascitis
2- Dilated veins
3- Spider nevi
4- palmar erythema
5- xanthalasma
6- caput medusa
7- Bruising (from coagulopathy, hypersplenism)

6- Allagile Syndrome → Do cardiac examination or in pulmonary artery stenosis ↗

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* "evaluation should be undertaken in a stated approach"
بالترتيب الاولويات

↳ for e.g → sepsis has the priority over α1-antitrypsin deficiency (it can wait, but sepsis is more important to manage)

* Things that are important to manage 1st :-
- sepsis
- Billiary atrasia
- Metabolic Diseases

*Labs to order :- *

1- CBC → look for elevated WBCs (infection)
Hb levels

2- urinalysis & culture → to rule out urosepsis

3- TSH, T4 → hypothyroidism causes Jaundice

4- liver Function test → to assess for severe destruction

5- Stool analysis

6- ABGs → Acidosis in septic pts
Also Acidosis in inborn error of metabolism.

7- Screening for CF → by sweat chloride test

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8- PT / INR → for acute function of liver

9- α_1- antitrypsin level

↳ Its produced in the liver and functions in lungs

↳ If there's deficiency → the abnormal shaped α_1-antitrypsin accumulates in the liver causing cirrhosis.

↳ If there's complete absence → Nothing happens in the liver (only emphysema)

10- Albumin level → Its an indicator of liver function (hypoalbuminemia means that the problem in the liver is a long one)

11- glucose level → hypoglycemia is a very bad sign in liver pts.

↳ It means that glycogen isn't used to produce glucose → liver is totally destroyed

↳ so its an indication of liver transplant.

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* other Diagnosis :-

1- US → check for Gallbladder : absent GB after appropriate fasting indicates BA

↳ cord sign → echogenicity of GB is higher than the liver at level of porta hepatis (due to fibrosis)

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2- MRCP → non-invasive MRI to check the billiary tree, pancreas, GB
↳ to diagnose choledocal cyst

3- hepatobilliary centeography (HIDA scan) → its an isotope scan, indicates the uptake function of the liver & excretion
↳ It scans for hepatocyte or billiary problem

* If HIDA scan suggestive of BA maybe due to neonatal hepatitis

* If there's good uptake, abnormal excretion → very suggestive of BA

* If poor uptake & we can't know if its BA or not → we do liver biopsy or the golden standard cholangiogram

* Billiary Atrasia *

- 90% of BA are non-syndromatic
- 10% come w/ lateralization (like situs inversus, asplenia, Midline spleen, DextroCardia).

↳ these appear on Prenatal Us → If you see these, think of BA.

* γ-GT enzymes indicates function of Billiary tree, we depend on it in pediatric more than ALT, AST.

* Cause of BA is still unknown. But some say its viral infection from mom, or Antibodies from mom to baby. Drugs. Rota virus.

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*The fibrosis continues after Birth

*whenever you have Jaundice, hepatosplenomegaly & clay colored stool → its BA till proven otherwise

* percentage of BA of all cases of cholestasis is 49%
↳ so you need to diagnose & treat fast

*Always in ER pediatric, ask about color of stool.

* Mangment → kasai Procedure (hepato porto enterostomy)
↳ we remove the damaged bile ducts, then cut 40cm segment from the Jujenum, and attach it to replace the duct, it connects the liver and the rest of the intestine to drain bile.

*Allagile Syndrome *

- facial features :- - broad forehead
- deep set eyes
- small pointed chin

- presentation :- - cholestasis
- facial features
- Butterfly vertebrae
- CVS & ocular abnormalities
↓
not embryotoxin

* Autosomal dominant ..... → There's variable expression. it skips generations

-paucity → قلة
intrahepatic → داخل الكبد
Billiary tree

- Their presentation is late, Prognosis better than BA

- Most common indication for liver transplant → itching (pruritis) → They have bad school performance because of itching! ، don't sleep.

* Progressive familial intrahepatic cholestasis * PFIC *

↳ happens at level of transport of bile from hepatocyte to billiary tree.

* Malabsorption due to failure to transport bile (you need bile to absorb fat) → leads to steatorrhea

* There are 3 types → PFIC 1, 2, 3.
- PFIC 3 presents later than PFIC 1, 2

- PFIC 1 → presents with hearing loss

(a baby 3-4 years old, with steatorrhea, cholestasis, pruritis, steatorrhea, Diarrhea, hearing loss ⇒ PFIC 1)

- Also they're more liable for crohn's Disease

- high γ-GT in PFIC 3

- Alf-fetal protein is important to distenguish bet. PFIC 1 & 3

(the table is important # scenarios)

(e.g → Normal γ-GT, α-fetal protein is very high, cholestasis present at age of 4 months ⇒ PFIC 2)

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* Zellweger Syndrome *

- Its a Metabolic disease
- has facial features : - high forehead (not bossing)
  - flat face
  - broad nasal bridge
- Severe hypotonia
- patellar cyst

* usually die by age of 6 years

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* How to differentiate bet. Metabolic & Non-metabolic Causes of cholestasis :-

- a sick child, w/ cardiomegaly & seizure, Failure to thrive, dysmorphic feature, acidosis, persistant vomiting ⇒ Think of Metabolic diseases

* Galactosemia *

- abnormal metabolism of Galactose
- Present in 1st 2-3 weeks
- Failure to thrive, vomiting, Diarrhea, Jaundice, hepatomegaly
- high ALT, AST,
- Ascitis, liver failure
- Cataracts → pathognomonic
- E. coli Sepsis

* Dx → reducing substances in urine
- Galactose 1 phosphate is high
- Mangment → Lactose free formula

* Tyrosinemia * (Fructose intolerant)

- hepatosplenomegaly, coagulopathy
- later presentation than galactosemia

- Manifest as - vomiting, Diarrhea, Jaundice, ascitis, Sepsis,

*weaning (feeding solid substances) → begins at 4m

↳ If you feed this pt an apple → Severe Diarrhea, vomiting, cholestasis, very sick looking child.

→ present at age of weaning.

Mangment of cholestasis * لازم *

1- high caloric Diet (for failure to thrive)

2- Medium chain Triglyceride (bcuz they don't need bile to be absorbed.)

3- Lipid soluble vitamins replacement