MARROW

2024 NEET-SS

UPDATED PEDIATRICS NOTES

GASTRO

APPROACH TO NEONATAL CHOLESTASIS

Active space

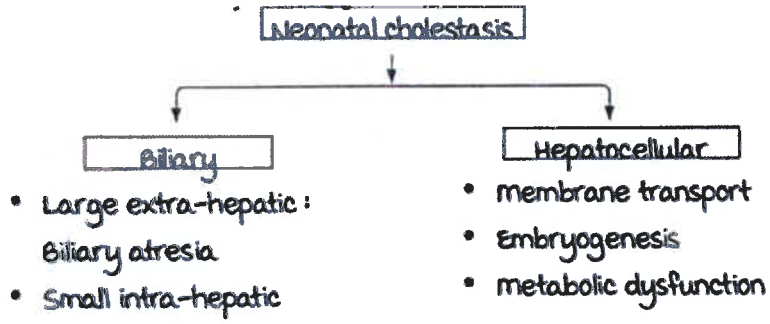
Introduction 00:00:36

High coloured urine staining diapers : Suspected cholestasis.
Incidence : 1 in 2500 live births.

Definition of cholestasis :

- Direct bilirubin > 1mg/dL (Total bilirubin < 5mg/dL).
- Direct bilirubin > 20% (Total bilirubin > 5mg/dL).
- First 5 days : Conjugated bilirubin > 0.5mg/dL or > 10%.

Etiology of cholestasis :



Clinical presentation :

- Biliary causes : High colored urine, pale stools, hepatosplenomegaly, less synthetic dysfunction.
- Hepatocellular causes : Synthetic functions of liver are affected (Can lead to liver failure in severe cases).

Etiology	
Anatomic obstruction	• Biliary atresia • Choledochal cyst • Inspissated bile plug syndrome • Spontaneous perforation of CBD
Toxic	• Sepsis • TPN associated cholestasis (TPN ≥14 days) • Drugs (Ceftriaxone >14 days)
Endocrine	• Hypothyroidism • Hypopituitarism

Feedback

Active space

Etiology	
Infections	• HSV (Herpes Simplex Virus) • Rubella • CMV (Cytomegalovirus)
Immune	• Gestational alloimmune liver disease • Hemophagocytic lymphohistiocytosis • Autoimmune hemolytic anemia-giant cell hepatitis
Genetic/ metabolic	• Galactosemia • Tyrosinemia • Alagille syndrome • Progressive familial intrahepatic cholestasis • Mitochondrial hepatopathies (multisustem involvement) • Bile acid synthetic defect (BASD) • HFI (Hereditary fructose intolerance) • Citrin deficiency • Urea cycle defects • Peroxisomal disorders • Neimann Pick type C • CESD/Wolman disease • Neonatal sclerosing cholangitis (Intrahepatic biliary drug involvement) • Congenital hepatic fibrosis • Cystic fibrosis

Perforation of CBD :

- Spontaneous or secondary to choledochal cyst.
- Presentation : Jaundice followed by ascites and disappearance of jaundice.

HSV causing cholestasis :

- Risk factor : mother affected with HSV.
- Can lead to liver failure.

Galactosemia :

Presentation : Cholestasis, sepsis, hemolysis, nausea and vomiting, cataract.

Screening test : urine for non glucose reducing substance.

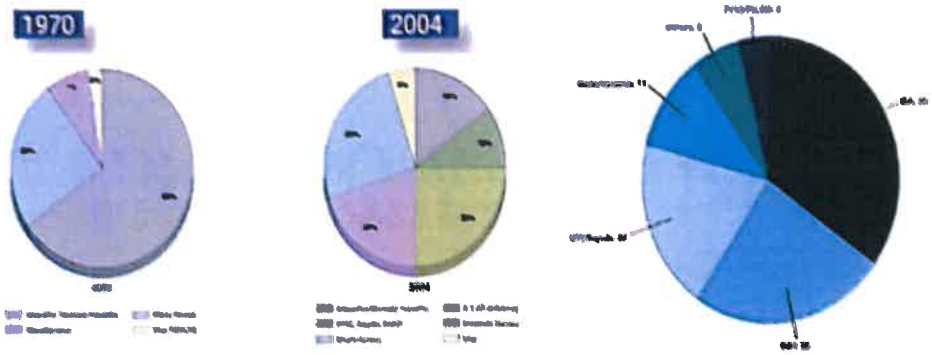
Confirmatory test : Enzyme levels in blood.

Tyrosinemia : Fetal cirrhosis.

Cholestasis with low/normal gamma glutamyl transferase (GGT) :

- Progressive familial intrahepatic cholestasis.
- Bile acid synthetic defect (BASD).

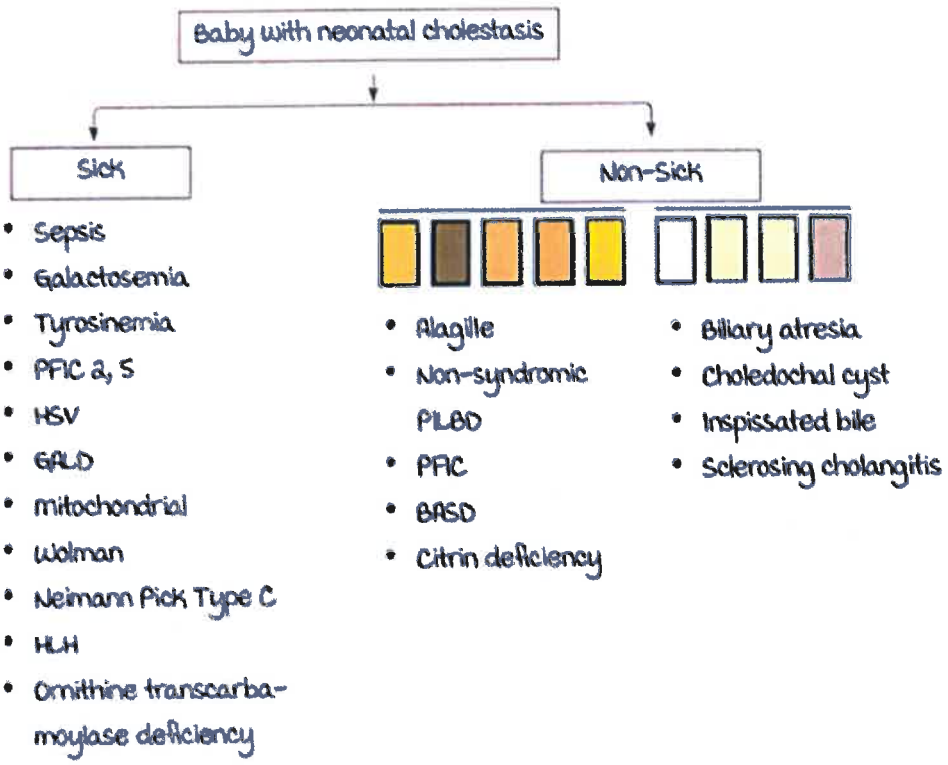
Changing etiology of neonatal cholestasis :



Indian study.

Approach to neonatal cholestasis 00:16:23

Traditional approach to neonatal cholestasis :



Active space

Neonatal cholestasis with pale stools :

Pale stools :

- Consider Biliary atresia.
- Can be d/t other causes.
- HIDA scan : Non-excretory.

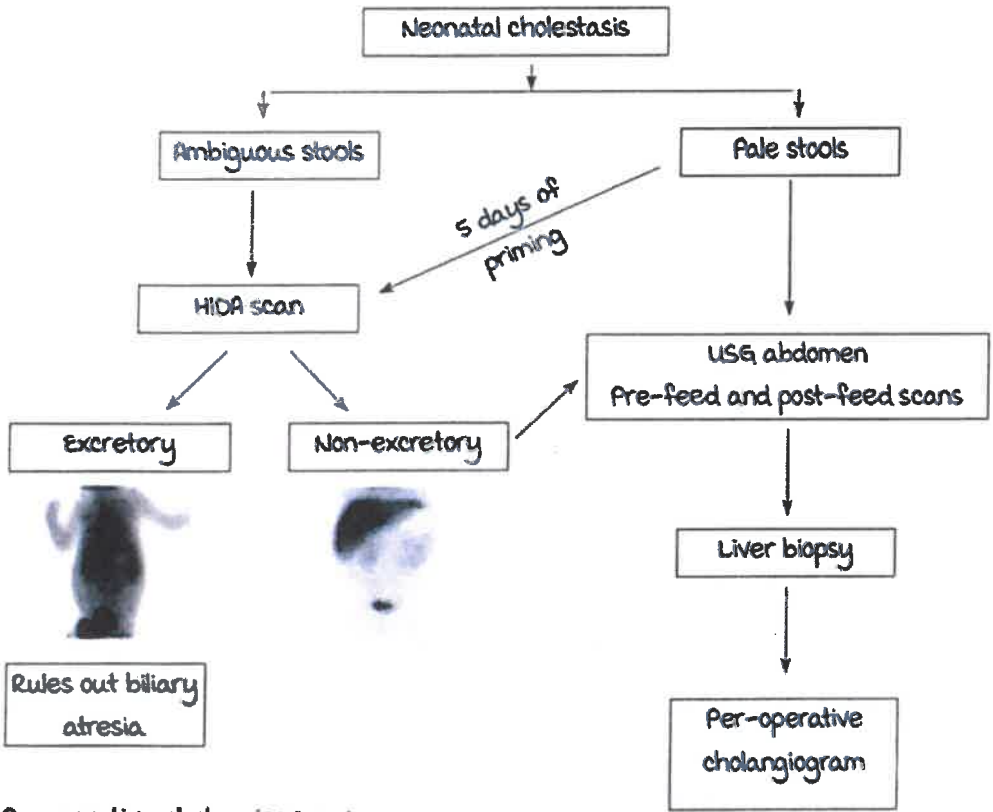
Ambiguous stools : Indication for HIDA scan.

Stool specimen : Should include core of the stool.

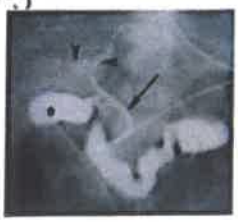
Pale stool

Pigmented stool

Classical pale stools.



Peroperative cholangiogram :



Normal

Cystic form of biliary atresia.

Role of gamma glutamyl transferase (GGT):

Neonatal cholestasis with pigmented stools.

Low GGT	High GGT
• Progressive familial intrahpatic cholestasis Type 1/2/4/5/6	• Alagille syndrome
• BRSD	• Paucity of intrahepatic bile ducts
• ARC syndrome	• Sclerosing cholangitis
• Hypopituitarism	• TPN associated cholestasis

ARC syndrome : Renal dysfunction + cholestasis + arthrogryopsis.

Note : No need of HIDA scan in case of pale stools.

Sick baby with cholestasis :

- Lethargy.
- Poor feeding.
- Seizures.
- Sepsis.
- Hypoglycemia.
- Coagulopathy (Uncorrectable by Vitamin K).
- Ascites.
- H/O sibling death with neonatal cholestasis.
- Poor weight gain.

Investigations in biliary atresia

00:26:19

Ultrasonogram in biliary atresia :

- Absence of gall bladder (Pre-feed).
- Size of gall bladder (<15 mm).
- Irregular echogenic walls.
- Triangular cord sign > 4mm at porta-hepatis.
- Gall bladder contractility post-feed (<60%).
- Cyst at porta with anechoic content.
- Increased hepatic artery sub-capsular flow.

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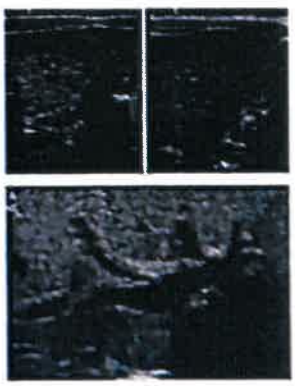


USG in biliary atresia.

Active space

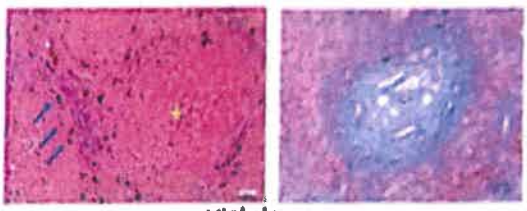
Role of percutaneous cholecystogram :

- 22 – 25 G needle.
- Technical success : 82%.

Percutaneous cholecystogram.

Histology in biliary atresia :

- Widening of portal tract.
- Ductular proliferation.
- Portal fibrosis.
- May be associated with ductal plate malformation.
- If equivocal ↑ biopsy at < 6 weeks of age, then repeat at > 6 weeks.



Histology.

CMV associated biliary atresia 00:30:11

It is highly controversial,lacking evidence so delays referral.

Pathogenesis :

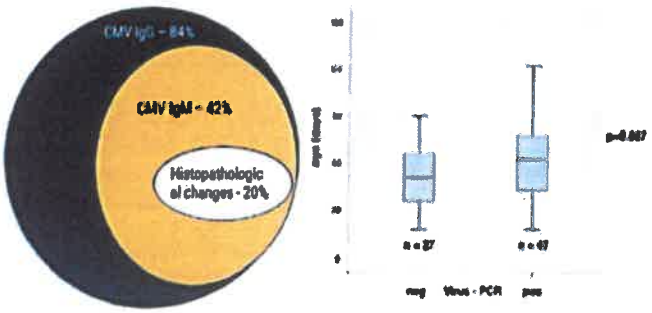
Earlier proposed pathogenesis : Perinatal CMV at birth leads to duct obliteration.

Latest theory :

- It is a confounding factor, innocent by stander.
- CMV affects T cell regulation, induces autoimmunity.
- Exagerrates ongoing duct injury.

CMV-Red herring study :

- IgM CMV positivity does not mean active liver replication.
- Mandatory to demonstrate CMV DNA by PCR or culture ± histological changes in the liver.
- No difference in outcome of IgM CMV (+ve) and CMV (–ve) biliary atresia.
- No improvement with ganciclovir.



Management of biliary atresia

00:32:55 Active space

Early diagnosis is key.

Definitive management :

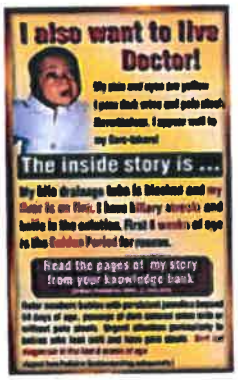
- Kasai portoenterostomy.
- Should not be delayed by CMV treatment.

Age of presentation (in days)	n (%) (n = 64)
< 30	6 (9.4)
30-45	12 (18.7)
45-60	26 (40.6)
60-90	14 (21.9)
> 90	6 (9.4)

Age at Kasai (days)	Native liver survival at 15 years (%)
31-45	40%
46 – 60	33%
61 – 75	28%
76 – 90	16%
> 90	13%

Yellow Alert Campaign – India :

- misdiagnosed as physiological/breast milk jaundice.
- False impression of well being to parents.
- Lack of awareness for referral



Neonatal liver failure

00:39:05

Conventional definition (PALF) :

PT-INR > 2 (with or without encephalopathy).

PT-INR > 1.5 with encephalopathy.

Caveats :

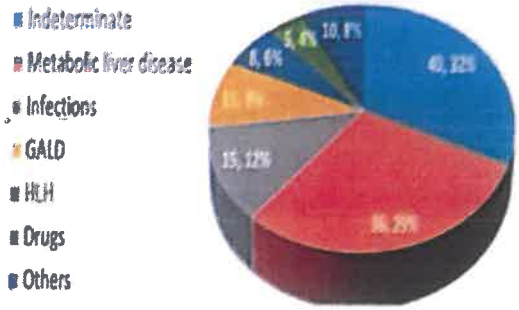
- Encephalopathy : Difficult to assess in newborns.
- PT-INR may be around 2 in newborns (Especially in preterm).
- Increase in bilirubin and transaminases : multiple causes.
- Neonatal acute liver failure : PT-INR >3.

modified criteria for neonatal liver failure : PT-INR >3.

Feedback

Etiology :

- metabolic liver diseases : 29%.
- Galactosemia : 17%.
- mitochondrial liver diseases : 7%.
- Urea cycle defect : 4%.
- Tyrosinemia : 4%.
- Neimann Pick type C : 3%.
- CDGIb : 1%.



Common causes of neonatal liver failure :

1. Neonatal hemochromatosis (GALD) : 15%.
2. HSV infection (12%).
3. HLH (Hemophagocytic lymphohistiocytosis) (3%).
4. Metabolic (25%) :
    - Galactosemia, Tyrosinemia, FAOD, HFI, BASD.
    - Mitochondrial hepatopathy, urea cycle defects.
    - Congenital disorders of glycosylation, Wolman's disease.
5. Bacterial sepsis (2%).
6. Hypocortisolism (2%).
7. Neonatal leukemia (1.5%).
8. Maternal drug (Paracetamol) overdosage (1.5%).
9. Indeterminate (36%).

Treatable causes in India :

Etiology	Treatment
Biliary atresia	Kasai portoenterostomy.
Choledochal cyst	Cyst excision and choledochoenterostomy.
Galactosemia	Lactose free diet.
HSV	Acyclovir.
Inspissated bile plug	Biliary irrigation.
GALD	IVIg, double volume exchange transfusion (DVET).
Hypoptuitarism, hypothyroidism	Hormone replacement.
Cystic fibrosis	Pancreatic enzyme replacement.
TPN associated cholestasis	Lipid modification, enteral feeding advancement.
HLH	HLH protocol
Tyrosinemia	Nitisinone, phenylalanine free diet, screen for hepatocellular carcinoma (HCC).
Bile acid synthetic defects	Cholic acid, chenodeoxycholic acid.

Active space

Clues to etiology :

Antenatal history :

- Pruritus : Progressive familial intrahepatic cholestasis.
- Acute fatty liver, HELLP : Fatty acid oxidation defect (LCHAD).
- Diarrhoea, respiratory infections : Enterovirus.
- Oligohydramnios, megaplacenta : GALD.
- Ultrasonogram : Choledochal cyst, cystic biliary atresia.
- Genital vesicles : HSV infection.

Signs and symptoms in neonate :

- Dysmorphism : Alagille, Zellweger, Down's syndrome.
- Heart murmurs : Alagille syndrome, biliary atresia.
- Hypotonia : Mitochondrial, peroxisomal.
- Hypertonia : Urea cycle defects.
- Cataract : Galactosemia, congenital infections.
- Splenohepatomegaly : HLH, Neimann Pick Type C (NPC), leukemia.
- Eye movement abnormalities : Septo-optic dysplasia, NPC.
- Chubby cheeks : Citrin deficiency.

Jaundice onset :

- At birth or soon after (days) : GALD, HSV.
- Few weeks after birth : PFIC, galactosemia.
- Any point of time : Mitochondrial hepatopathy, HLH.

Seizures :

- Hypoglycemia : Galactosemia, mitochondrial hepatopathy, hereditary fructose intolerance, panhypopituitarism.
- Intracranial bleed : All conditions.
- CNS infection : HSV.
- Intoxication : Mitochondrial hepatopathy, congenital portosystemic shunts (CPSS), urea cycle disorders.

Early ascites :

- Galactosemia.
- GALD.
- Tyrosinemia.

Active space

USG :

- Gallstones : PFIC.
- Nephromegaly : Tyrosinemia, HFI.
- Abnormal vascularity : CPSS.
- Adrenal calcification : Wolman.

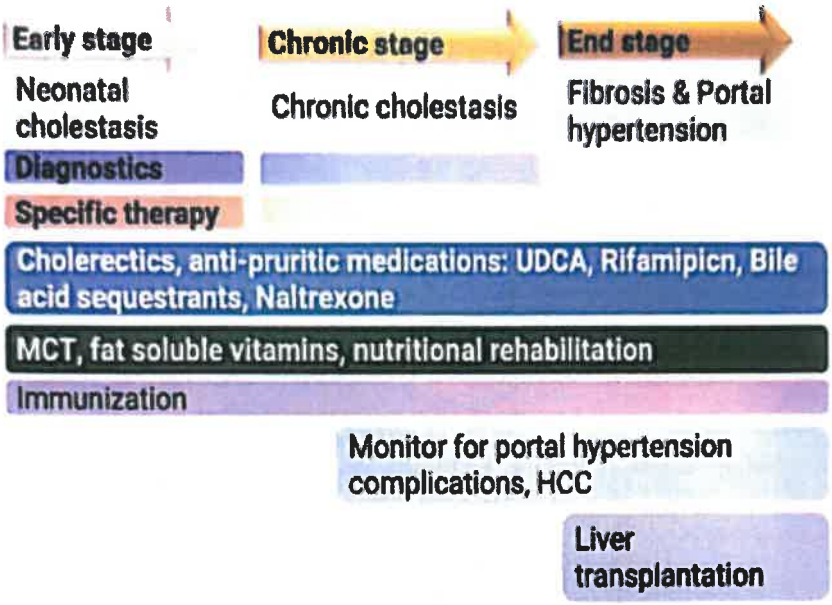
Investigations :

Condition	1st line investigation	Confirmatory tests
Galactosemia	Urine NGRS Galactose 1 phosphate uridyl transferase	Genetics (h/o blood transfusion)
Tyrosinemia	High AFP Urine succinyl acetone	Genetics
GALD	High ferritin High AFP	Lip biopsy MRI pancreas Liver biopsy C5b-9 staining
HLH	High triglycerides, ferritin Low fibrinogen, Low NK cell activity	Bone marrow Genetics
HSV	HSV PCR	
BASD	Low GGT Low bile acid level	Genetics
Neimann Pick -C	Urine chitotriosidase Bone marrow	Genetics

Initial treatment :

- MCT (medium chain triglycerides) supplementation.
- Ascites management : Diuretics.
- Prophylactic antibiotics.
- Avoid hypoglycemia.
- FFP (Fresh Frozen Plasma) : Only in case of bleeding.

Feedback



Holistic management.

Case discussion 00:55:40

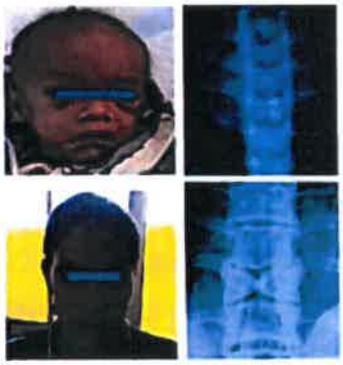
Case 1 :

a months/Baby boy presents with icterus at 20 days of life.

Fluctuating stool colour.

Examination findings :

- Liver 4cm BCM, firm.
- Spleen 3cm BCM.
- No ascites
- Systolic murmur in right axilla.
- Facies : Pointed chin, pointed forehead.
- Butterfly vertebra in mother and baby.



Investigations :

Bilirubin (mg/dL) : 15/10.5

AST/ALT (IU/L) : 119/152

Albumin (g/dL) : 4

GGT (IU/L) : 378

INR : 1.02

Echo : Peripheral pulmonary stenosis.

Ophthalmological examination : Iris hypoplasia.

Active space

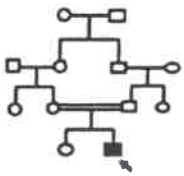
Liver Biopsy :

- Paucity of bile ducts.
- Bile duct to portal tract ratio 0.2.
- Number of portal tracts : 6.

Diagnosis : Alagille syndrome.
Mother: Same mutation (Autosomal dominant).

Gene (Transcript) *	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
JAG1 (-) (ENST00000254958.5)	Exon 23	c.2698C>T (p.Arg900Ter)	Heterozygous	Alagille syndrome	Autosomal dominant	Pathogenic

Case 2 :
4 months/baby boy presented with jaundice with high colored urine from 1 month of age and pruritus from 3 months of age.
Intermittent pale stool.
H/o skin bleed at 2 months age.
No encephalopathy, ascites.
No h/o pruritus in the mother during pregnancy.



Consanguineous marriage.

Differential diagnosis :

- Progressive familial intrahepatic cholestasis.
- Alagille syndrome.
- Sclerosing cholangitis.

Investigations :
Bilirubin (mg/dL) : 10/6.5.
AST/ALT (IU/L) : 460/252.
Albumin (g/dL) : 4.
GGT (IU/L) : 50.
INR : 1.02.

USG abdomen :
Biliary system normal.
No splenomegaly, kidneys normal.

Alagille workup : Negative.
Echocardiography, X ray dorsal spine, eye examination

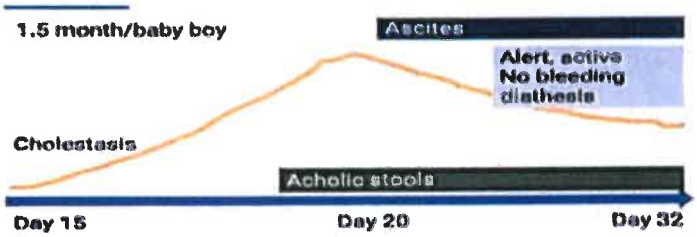
Liver biopsy :

- Bland cholestasis.
- Maintained lobular architecture.
- No bile ductular paucity.

Clinical exome sequencing : ATP8B1 mutation positive.

Diagnosis : PFIC I.

Case 3 :



Investigations :

Total bilirubin/direct bilirubin (mg/dL) : 5/3.2.

AST/ALT (IU/L) : 8/93.

SAP/GGT(IU/L) : 655/473.

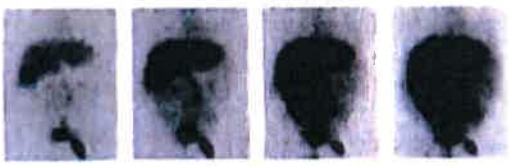
Total protein/albumin (g/dL) : 5.5/3.5.

PT-INR : 1.2.

Ascitic fluid :

- Deep yellow.
- Bilirubin level : 20mg/dL.

HIDA scan : Confirmed bile leak.



HIDA scan showing biliary leak.

Laparotomy : Perforation at insertion of cystic duct.

Management :

- Peritoneal drainage.
- Cholecystostomy.

CHRONIC LIVER DISEASE

Active space

Etiology of CLD

00:00:40

Biliary diseases :

- Biliary atresia.
- Choledochal cyst.
- Sclerosing cholangitis.
- Progressive familial intrahepatic cholestasis (PFIC).
- PILBD.
- Alagille syndrome.
- Bile acid synthetic deficiency.

Intrahepatic causes :

- Wilson disease (m/c).
- Autoimmune liver disease.
- HBV/HCV (HAV & HEV never causes CLD).
- Budd-chiari syndrome.
- Congenital hepatic fibrosis.
- Storage diseases (Niemann-Pick, Gauchers) : Infiltration leads to fibrosis.
- NAFLD/meFLD.

Metabolic diseases :

- Tyrosinemia (A/w HCC).
- Galactosemia, hereditary fructose intolerance.
- Indian childhood cirrhosis (incidence is decreasing).
- Congenital disorder of glycosylation.

<5 yrs of age	>5 yrs of age
• Biliary atresia. • Choledochal cyst. • PFIC. • Alagille syndrome. • Galactosemia. • Tyrosinemia type I. • Indian childhood cirrhosis. • Glycogen storage disease IV. • Bile acid synthetic defects. • Cholesterol ester storage disease.	• Autoimmune liver disease. • Wilson disease. • Hepatitis B virus. • Sclerosing cholangitis (Ass. with UC). • Tyrosinemia type I. • Alagille syndrome. • PFIC class III (↑ GGT). • Niemann-Pick disease type C. • Glycogen storage disease III. • Non-alcoholic fatty liver disease. • Choledochal cyst.

Active space

Clinical presentation

00:14:47

Suspicion of CLD :

Clinical :

1. Features common to all :
   - Physical features of liver.
   - Evidence of portal hypertension.
   - Stigmata of CLD.
   - Decompensation.
2. Features specific to etiology :
   - Wilson disease : KF ring.
   - AIH : Other autoimmune features.
   - PSC : Bloody diarrhea.

Investigations :

- Low albumin.
- Uncorrectable coagulopathy.
- Varices on endoscopy.
- Dilated portal vein.
- Abdominal collaterals.

Types of presentation :

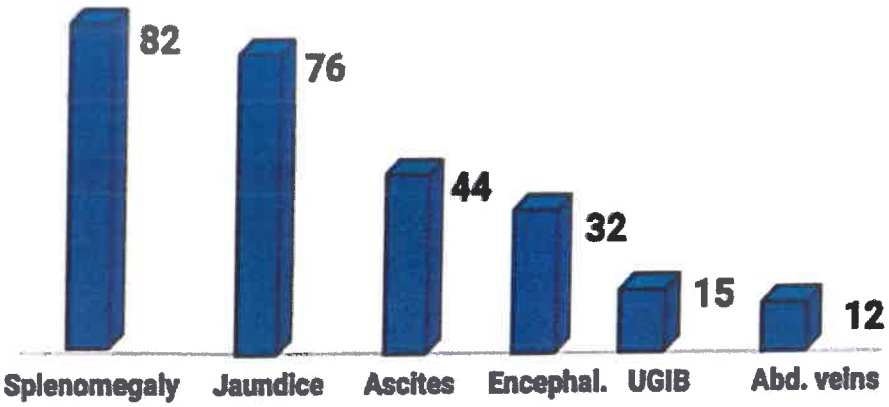
1. Florid presentation of chronicity.
   (Decompensated liver disease).

2. Subtle presentation or long duration.
   Clinical features of chronicity.

3. Acute presentation at onset.
   Acute hepatitis on underlying CLD (Acute on chronic liver disease).

Presenation 1 : Florid manifestations of CLD

- Jaundice (Conjugated).
- Ascites. } Decompensated LD
- Encephalopathy. } Decompensated LD
- Variceal bleed.



Frequency of clinical features in children with cirrhosis

Presentation 2 : Subtle features.

- Jaundice (Conjugated & short duration).

AND

- Transient ascites resolved.

OR

- Altered sensorium recovered.

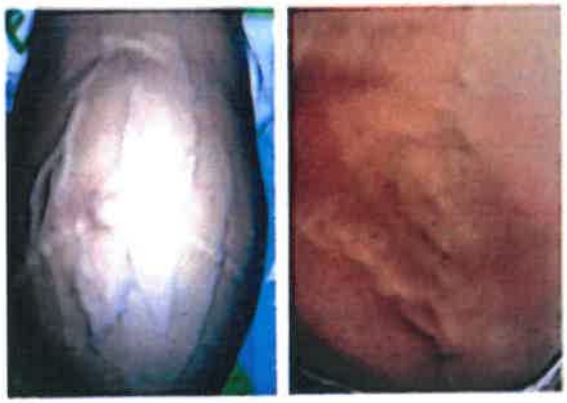
To diagnose, look for :

Feature	Comments
Liver margins.	• Sharp and irregular ("Leafy" in Indian childhood cirrhosis).
Liver surface.	• Nodular. Eg : Tyrosinemia, hepatitis B (Post-necrotic macronodular cirrhosis).
Liver consistency.	• Firm is not specific (Probable). • Hard in congenital hepatic fibrosis.
Liver span.	• Shrunken specific for cirrhosis. • Enlarged in cirrhosis due to secondary biliary causes, cholestatic diseases on infancy, storage disorders.
Differential enlargement.	• Left lobe larger than right lobe.

Signs of portal hypertension :

- Splenomegaly.
- Free fluid (Ascites).
- Tortuous veins (Abdomen; back).

Active space



Caput medusa.

Diagnostic paracentesis :

- Deranged INR is not a contraindication.
- Determine SAAG.
  SAAG > 1.1 : Ascitis is d/t portal HTN.
- Check for infection : TLC, DC, culture sensitivity.

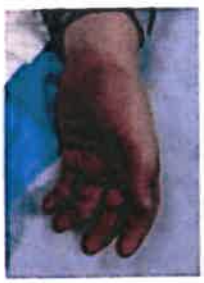
Evidence of portal hypertension in CLD :

- Collaterals veins in anterior abdominal wall.
- Upper GI bleeding.
- Ascites.

Confirmation by imaging.

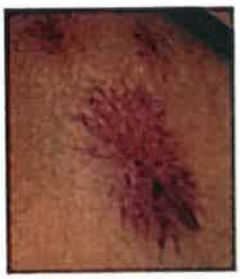
Stigmata of CLD :

Effect of the synthetic function of CLD or hormonal imbalance.

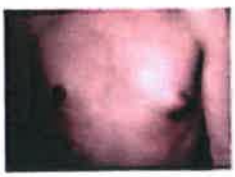


Palmar erythema.

Clubbing.



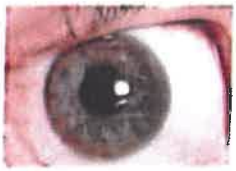
Spider nevi.



Gynaecomastia.

Other features :

Bitot spots.



KF Ring.

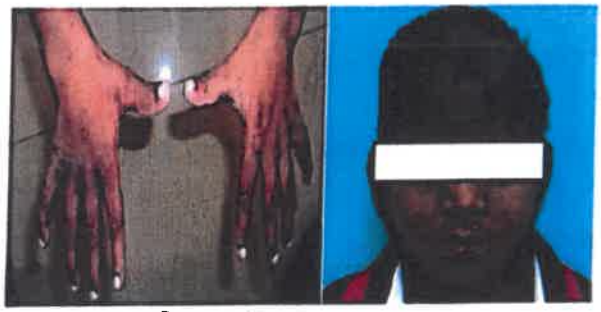
Alagaille syndrome.

Rickets.

Presentation 3 :

Pruritus :

- Long standing.
- Early onset.
- Intractable.
- Familial.



Lichenification.

Jaundice (Conjugated) (Irrespective of duration) :

- Persistent or
- Recurrent.

Presentation 4 : Subtle manifestations.

- Family history of CLD.
- Obesity.
- Systemic features :
  - I. Rash.
  - II. Joint pains.
  - III. Acne.
- Multi-transfused.

Leads to : Elevated of liver enzymes & hepatosplenomegaly.

Presentation 5 : Asymptomatic

Asymptomatic elevation of

- Transaminases.
- Alkaline phosphatase.
- Gamma glutamyl transferase.

On examination :

- Hepatosplenomegaly.
- Shrunken liver.

Management :

- Observation.
- USG scan.

Investigations

00:38:19

Step 1

Investigations to be done :

- LFT including GGT.
- Hemogram (To check for hypersplenism related cytopenia).

Note :

If transaminases 2-3 times ULN ± other abnormality, rule out the following :

- No recent concurrent illness (Infection).
- No recent or concurrent drug therapy (Hepatotoxic).
- No transfusions in the last 6 months.
- No AVH in last 6 months.
- No cardiac disease.

Document persistence > 3 months, multiple times.

Step 2

If hepatomegaly ± splenomegaly present : USG of Hepatobiliary, HV, IVC.

Other investigations as per etiology :

- HBsAg.
- Anti-HCV.
- For Wilson disease : Serum ceruloplasmin, 24 hr urinary copper, KF ring.
- For AIH : ANA, SMA, LKM-1, IgG .
- Lipid profile if obese.

Lastly, liver biopsy : Percutaneous unless contraindicated.