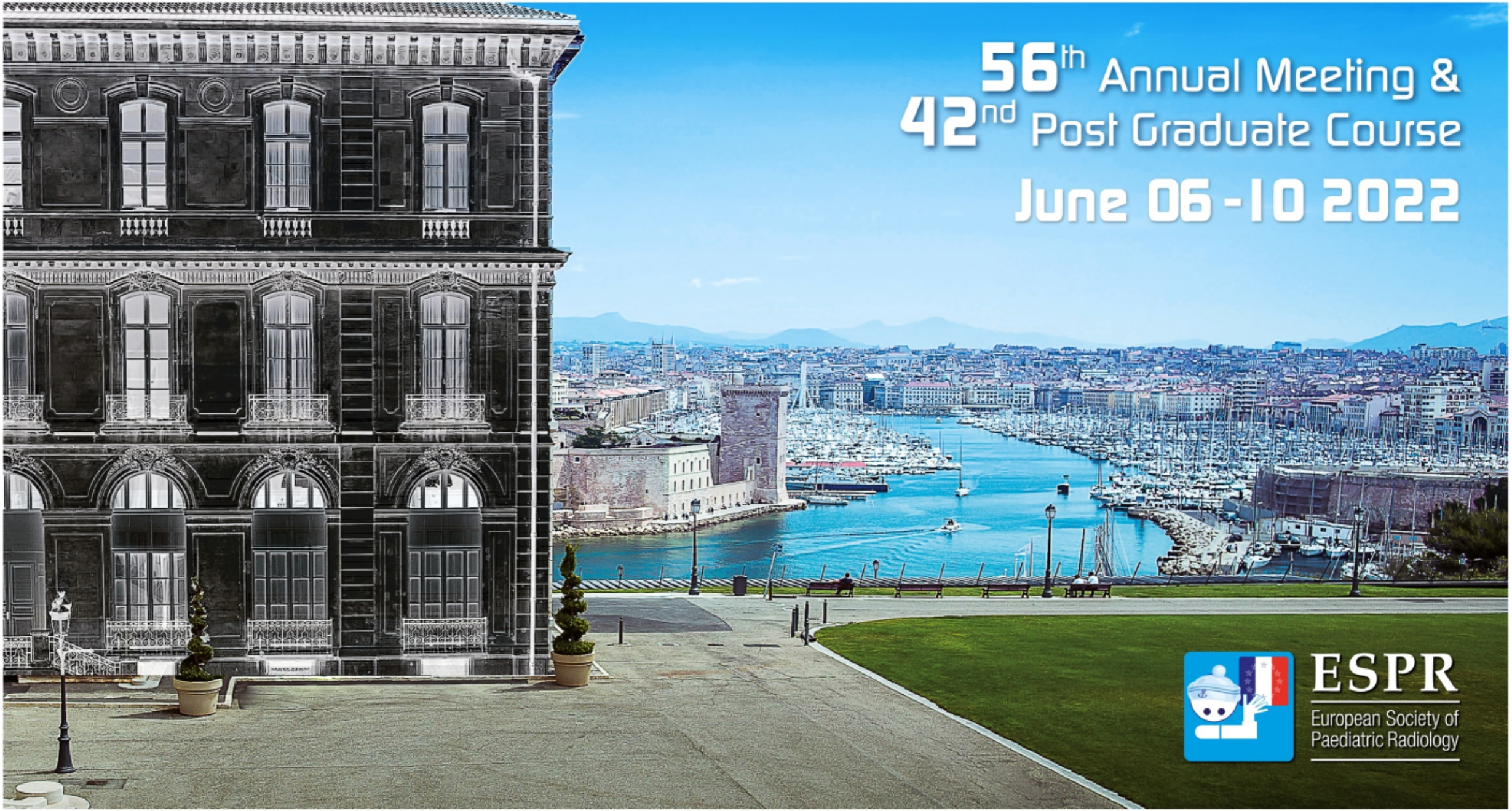
56th Annual Meeting &
42nd Post Graduate Course
June 06 - 10 2022
ESPR
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filière de santé maladies rares

AVB-CG CENTRE DE RÉFÉRENCE ATRÉSIE DES VOIES BILIAIRES ET CHOLESTASES GÉNÉTIQUES

MVF CENTRE DE RÉFÉRENCE MALADIES VASCULAIRES DU FOIE

MIVB-H CENTRE DE RÉFÉRENCE MALADIES INFLAMMATOIRES DES VOIES BILIAIRES ET HÉPATITES AUTO-IMMUNES

CRMR Maladie de Wilson et autres maladies rares liées au cuivre

Pediatric pathologies leading to cirrhosis: How the GI pediatrician identifies the causes.

HCL HOSPICES CIVILS DE LYON

Dr Noémie Laverdure MD, MSc

Hopital Femme Mere Enfant - Lyon

Université Claude Bernard Lyon 1

Conflict of interest

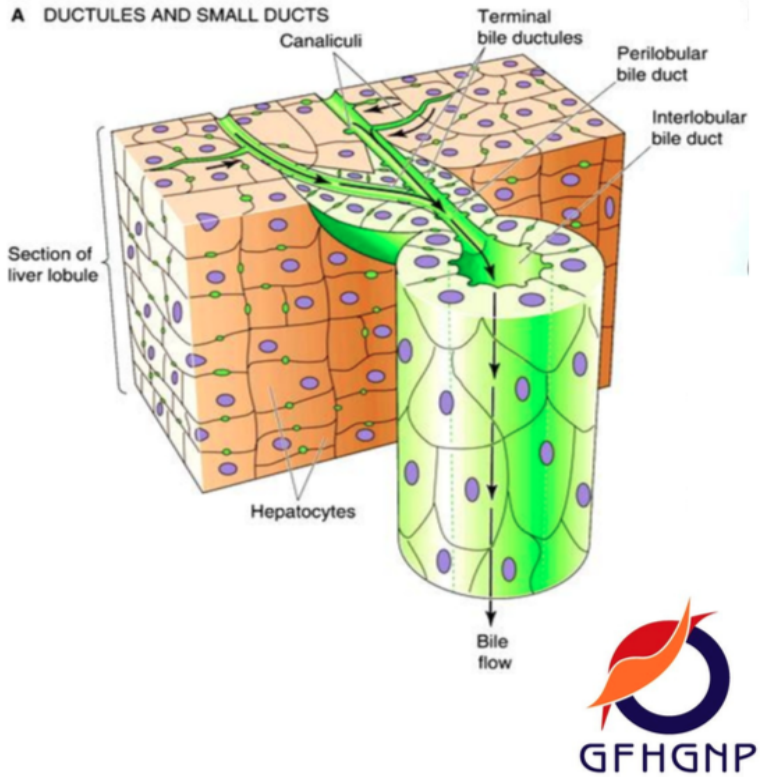
- None related to the subject

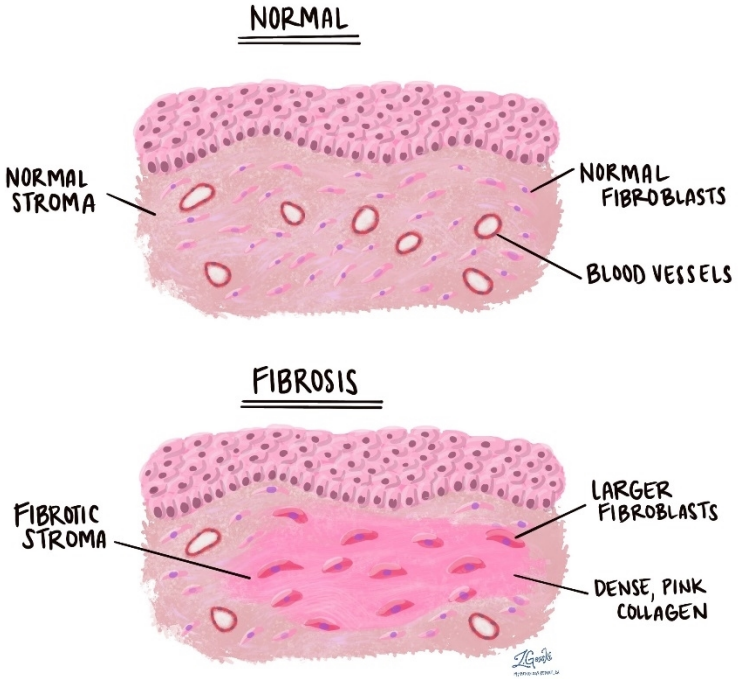
About what?

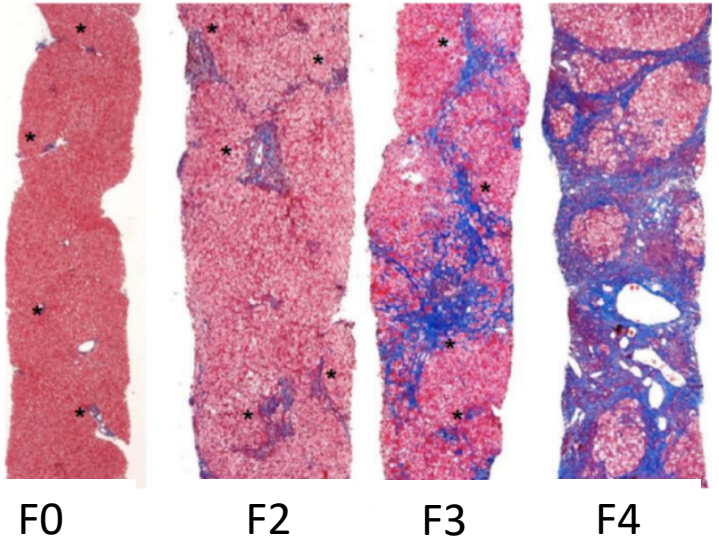
- Cirrhosis generalities
- Neonate vs Children
  - Neonatal cholestasis
    - What do we expect from radiology/st?
    - Intra and Extrahepatic
    - Intrahepatic
- And in children?
  - Presentation mode
  - Virus
  - Auto immune
  - Genetic
  - Metabolic disorders
  - Vascular

Cirrhosis Generalities 1/2

- Dynamic process from fibrosis to cirrhosis
- F0 to F4

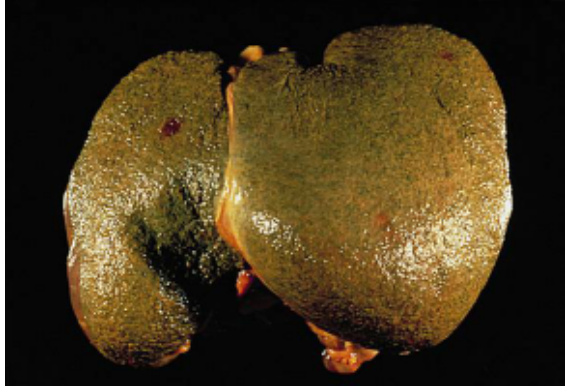






From : gfhgnp; https://www.mypathologyreport.ca/fr/fibrosis/

Cirrhosis Generalities 2/2



- Complications :
  - Portal Hypertension (OV, ascitis, Pshunt…)
  - HCC
  - Hepatocellular dysfunction

- Etiology (adult)
  - Alcohol
  - HBV, HCV
  - NASH

- Diagnosis
  - Histologic (liver biopsy)
    - Percutaneous or transjugular
    - gastro/radio/surgeon
    - Local habits, Biology
    - Minimal 10 Portal Triad
  - Non invasive tests (elastometry, biological scores..)

Gold standard

- Treatment
  - Etiology
  - Of complications
  - Nutritionnal support
  - Liver transplantation

Neonate vs Children

Different presentation mode :

- Children : cirrhosis/complications could reveals the disease
- Neonate : neonatal cholestasis ++

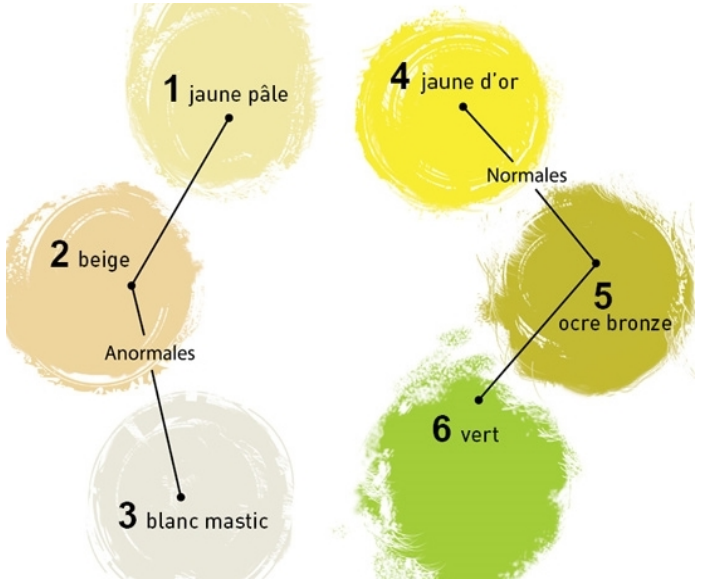
Neonatal Cholestasis

Presentation

- Neonatal jaundice
  - > 15 days

- +/- Decolorated stools
- Dark urines
- No pruritus before 4 months

EMERGENCY !



Stools colorimetric scale

- 1/2 500 births

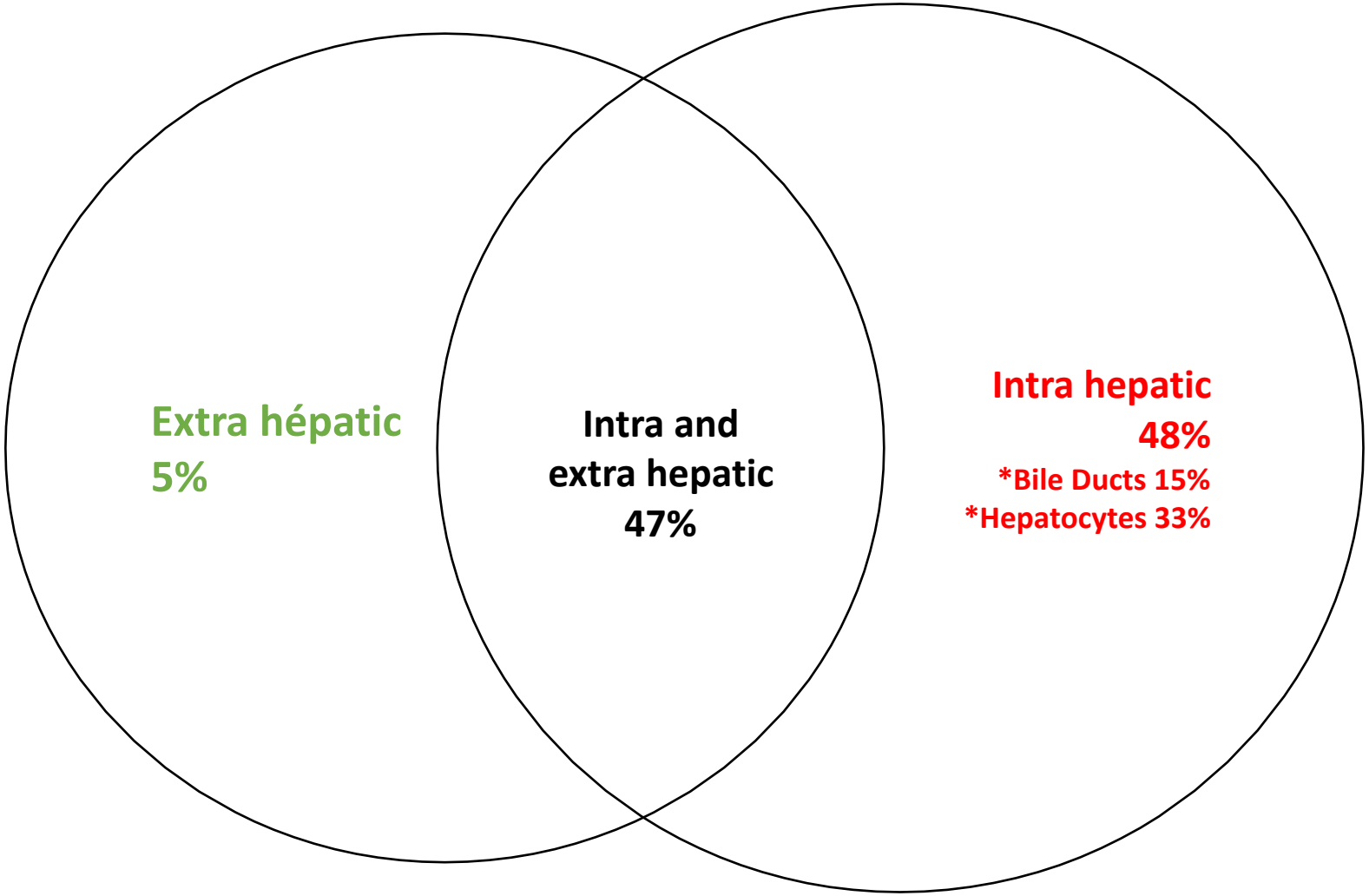
Clinic / Exams

- Familial/Personnal History
  - Consanguinity?
  - Familial liver diseases?
  - Lithiasis? Cholecystectomy?
  - Pruritus/cholestasis during pregnancy?
  - Birth
- Clinic
  - Hepatomegaly? Splenomegaly?
  - Facial dysmorphy?
  - Ascitis?
  - Hypoglycemia?
  - Neurological delay

- Biology
  - AST/ALT
  - GGT (N or ↑)
  - Bilirubin : total/conj
  - PT / FV

+++ Vit K IV/IM

Etiology = Many!



What do we expect from radiology/st?

First : US exploration

- General morphology
  - Situs inversus? Multiple spleen? Preduodenal portal vein ? mesenteric vessels ?
  - Splenomegaly?
  - Signs of portal hypertension
- Liver
  - Morphology
  - Hilum Kyst, Triangular cord sign
  - Atretic vesicle, irregular
- r/o **extra hepatic etiology** = bile duct dilatation
  - Lithiasis?
  - Congenital dilatation of principal biliary duct?

WARNING
Non significant if US
< 8-10h post meal

Intra and extra hepatic

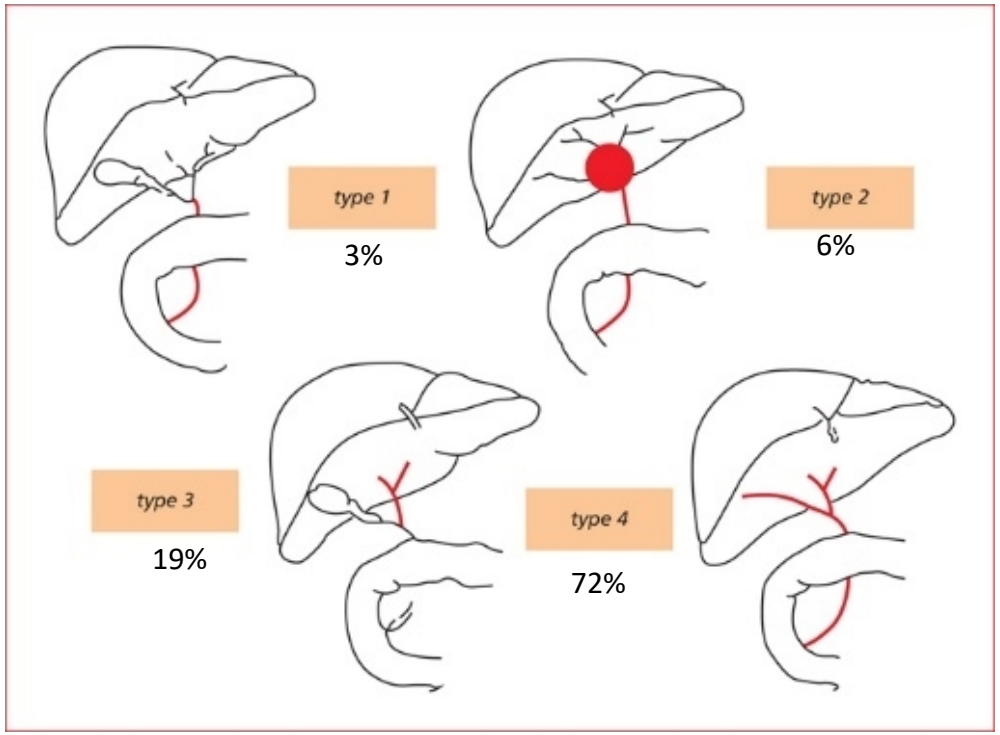
Biliary atresia 1/4

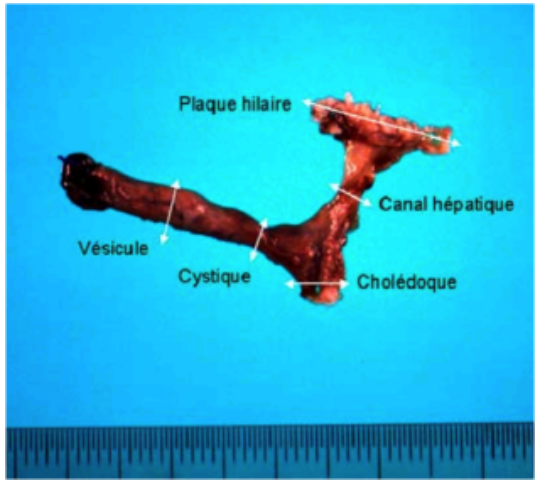
THE NEONATAL EMERGENCY

- First indication of liver transplantation in children
- 50% of neonatal cholestasis
- 1/18 000 births
- Progressive obliteration of bile ducts
  - Etiology : unknown
  - Before (10% - syndromic forms) or just post birth

Biliary atresia 2/4

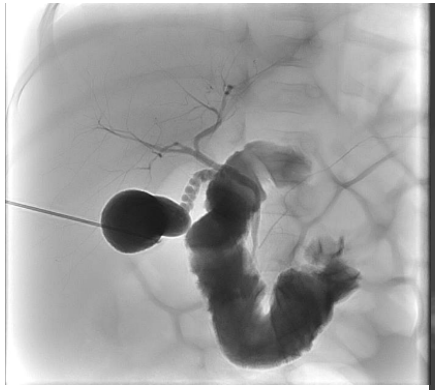
- Anatomic forms



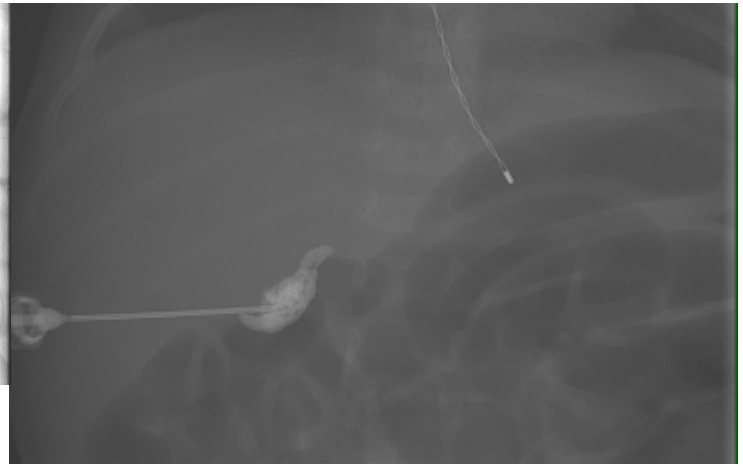


From : Chardot et al JHepatol 1999 - Okubo et al Hepatol Commun 2020

Biliary atresia 3/4



Ductopeny



Biliary atresia

- Diagnosis
  - Could be evocated on US
    - Normal US don’t eliminate the diagnosis
    - US could show if percutaneous cholangiography is possible
  - Cholangiography (+ biopsy)

Percutaneous
Radiologist
- : interventional radiologist
2 times procedure if confirmation
+ : less invasive procedure

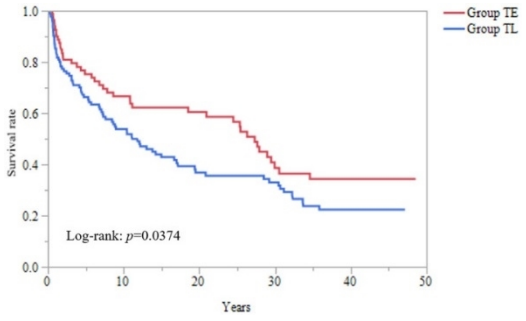
Endoscopic
Gastroenterologist
- : specific material
Not in all centers
2 times procedure
+: less invasive procedure

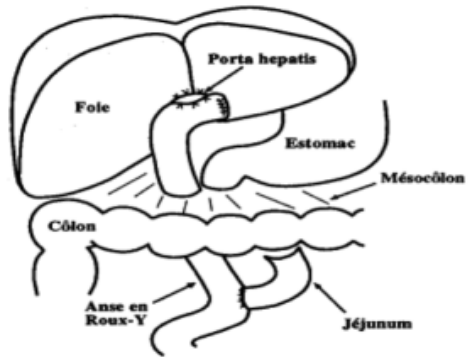
Surgical
Surgeon
- : scar/invasive
+ : 1 general anesthesia : Kasai surgery in the same time if diagnosis is confirmed
Portal pressure evaluation

Choice : among availability of procedures level of suspicion and age (old > surgical)

Biliary atresia 4/4

- Treatment
  - Without = Death <3yo
  - Kasai surgery
    - Hépatoportoentérostomy
    - Hépatoportocholécystostomy
    - Kystojéjunostomy
  - Early is better +++

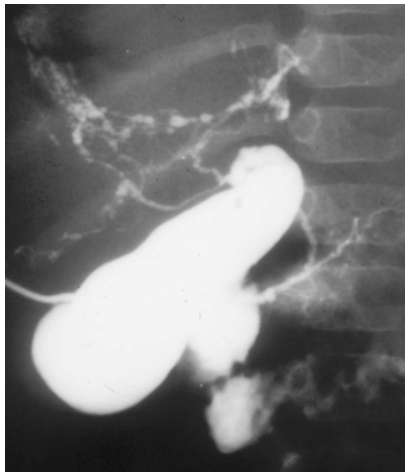




From : Chardot et al JHepatol 1999 - Okubo et al Hepatol Commun 2020

- Follow up : US++
  - Progressive evolution ad cirrhosis
    - Progression of portal hypertension :
      - Portal flux / inversion/ thrombosis
      - Ascitis
      - Splenomegaly
      - Digestive varices – spontaneous shunts
    - Liver morphology : biliary kysts, HCC !
- Emergency
  - oesophageal varices bleeding and TIPS : rare in children

Neonatal sclerosing cholangitis



- 2,5% of neonatal cholangitis
  - Neonatal cholestasis > +/-regression > fibrosis > cirrhosis
- Diagnosis : cholangiography
- Histology :
  - High fibrosis
  - Bile ducts proliferation
- Familial history – genetic?
  - 50% consanguinity
  - Siblings
  - 60% extra hepatic disease associated
- + Ichtyosis
  - Claudin 1 mutation (tight jonction protein - cutaneous and inter hepato/cholangiocytes)

From : Debray et al JPediatr 1993; Hadj-Rabia S et al Gastroenterology 2004

Intra hepatic

More frequent/ First to eliminate

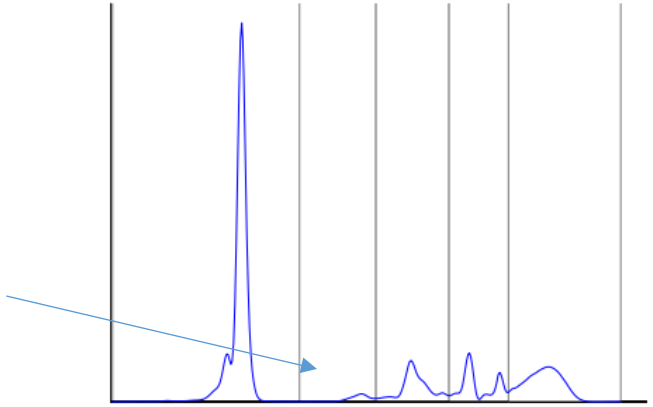
Urinary infection
E.Coli +++

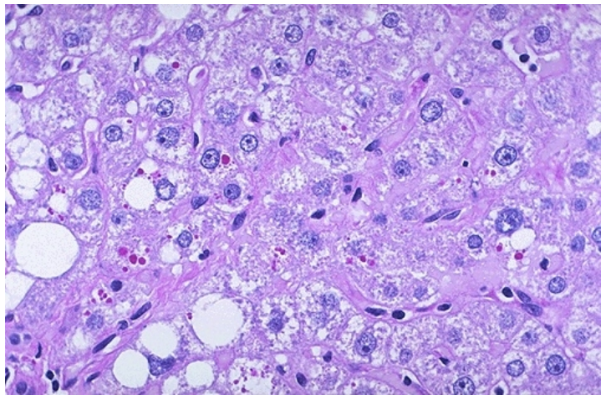
Cystic Fibrosis

- 1/3000 birth in Europe
- Diagnosis
  - Neonatal depistage
  - Sudoral chlore
    - Genetic
- CFTR mutation chr 7
  - delta F508 70%
  - Protein present on liver cells
- Mecanism
  - Loss of sodium > ↑ viscosity liquids
  - Dehydrated bile
- Clinic
  - +/- Associated with meconial ileus
- Evolution
  - Progressive fibrosis
  - Portal hypertension and complications
- Sometimes need for liver transplantation +/- pulmonary

Alpha 1 antitrypsin deficiency

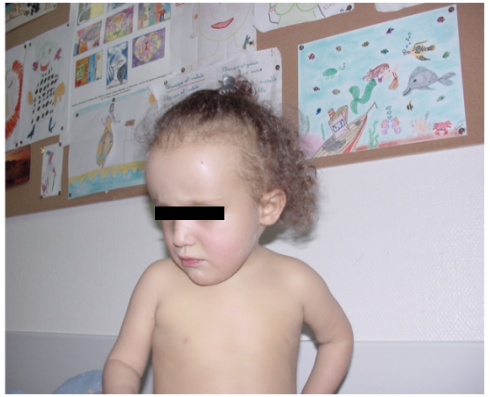
- 1/3500 birth
- Diagnosis :
  - a1AT <1.1 g/L
  - Phenotype : ZZ++
  - Genotype
- Serpina 1 chr 14
  - Folding disorder – liver toxicity/accumulation
- Histology
  - Periportal red hyaline globules PAS stain
  - Fibrosis
  - Steatosis



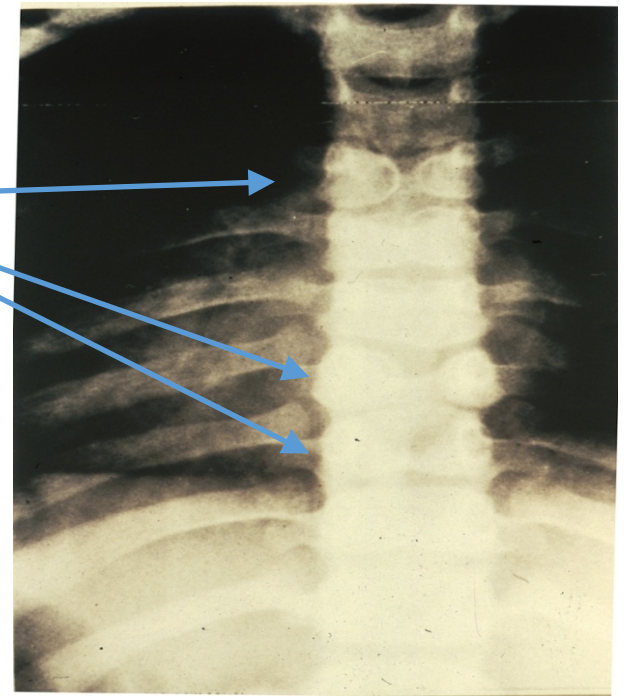


From : https://webpath.med.utah.edu/LIVEHTML/LIVER052.html

Alagille syndrom



- 1/70 – 100 000 birth
- Syndromic bile duct paucity
- Clinical critera 3/5
  - **Cholestasis**
  - Morphology : facial dysmorphy
  - Bone : butterfly vertebrae
  - Cardiac : Pulmonar artery stenosis
  - Ophtalmo : posterior embryotoxon
    - +/- Kidney : tubulopathy
    - +/- Vascular : anevrysma, thrombopathy
- Autosomic dominant : JAG1, NOTCH2



Intra hepatic

Other etiologies : HISTOLOGY Helps!

Progressive Familial Intrahepatic Cholestasis

- Genetic diseases – Recessive autosomic +++ - Type 1-6
- History
  - Consanguinity
  - Familial history of lithiasis
- Defect in canalicular transport proteins on hepatocytes
  - Imbalance in bile composition
  - Cholestasis, lithiasis, **pruritus**, diarrhea
- Biology
  - Normal GGT in PFIC 1-2 / increase in PFIC 3
  - Increased sera bile acids
  - Bile composition analysis
- Histology
  - Antibody stain for the differents proteins

Primary bile acid synthesis deficit

- Biology
  - Normal GGT
  - Low/normal sera bile acid
- Confirmation
  - Urines bile acid chromatography : accumulation of abnormal metabolites before the enzymatic deficit
  - Genetic
- Treatment
  - Cholic acid

Fœtal infections

- CMV, toxoplasmose, syphilis, german measle

- Clinic :
  - Intra Uterin Growth Retardation
  - Splenomegaly

- Biology :
  - PCR CMV (urines)
  - Maternal serology

- Other :
  - Radiography
  - Ophtalmologic exam

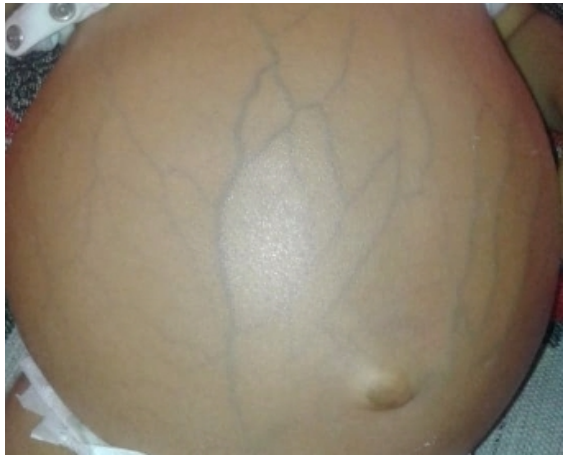
Metabolic disorders

- Mitochondrial Disorders
- Peroxysomal diseases
- Tyrosinemia
- Gaucher/Niemann-Pick

- Clinic
  - Extra hepatic manifestation (neurological)
  - Neonatal hypoglycemia
  - Hepatocellular dysfunction
  - Splenomegaly +++ (G/NP)
- Biology
  - Lactates ++
  - aFP (Tyr)
- Histology
  - steatosis

And in children ?

Presentation mode = various



- Clinic :
  - Acute or chronic / asymptomatic
  - Asthenia, anorexia, loss of weight
  - Jaundice, pruritus
  - Hepatomegaly, splenomegaly
  - Collateral circulation
- Complication : ascitis, digestive hemorrhage, fulminant hepatitis
- Liver tests abnormalities
  - ↑ AST/ALT +/- ↑ GGT
  - Albuminemia, glycemia, PT/FV
- US : hepatomegaly, splenomegaly, steatosis, HCC

Etiologies and radiological specificities

Virus

- Hepatitis B and C
- Mother to child transmission +++
  - Migrant
  - History of parent toxicomany
- Blood serology + PCR
- Radiology
  - HBV : HCC on non cirrhotic liver!
  - FU US : normal to cirrhosis, +/- signs of portal hypertension
- Non invasive FU of fibrosis
  - Fibroscan®

Auto immune

- Hepatitis – Cholangitis (IBD++) – Overlap syndrom
- Girl > Boy
- Adolescent +++
- <5 /10^5 children
- Biology :
  - Signs of portal hypertension
  - ↑Inflammatory syndrom
  - ↑ GGT
  - IgG
  - Autoantibodies +++ (AIH)
- Radiology
  - US
    - r/o other cause of abnormal liver tests
    - Signs of chronic disease (splenomegaly, signs of portal hypertension)
  - Bili –MRI
    - First exam for diagnose bile ducts lesions
- Histology
  - Liver biopsy
  - Non mandatory but fibrosis baseline
  - Giant cells, plamocytes
  - 50% AIH cirrhosis at diagnosis

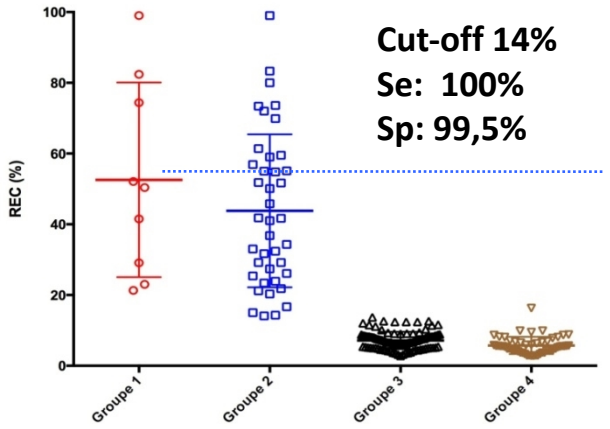
Genetic 1/2 - Wilson Disease

- 1/50 000 birth
- Autosomic recessive
- Chr 13 – ATP7B gene
- Cupper metabolism
- Familial history : consanguinity ++

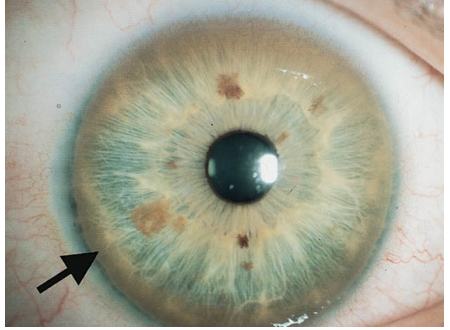
WD diagnostic ou inobservance	WD traités	Hépatopathies Adultes	Hépatopathies Enfants
53 +/- 27 (21,5-99)	44 +/- 22 (14-99)	7 +/- 2 (3-13,5)	6 +/- 2,5 (3-16,5)

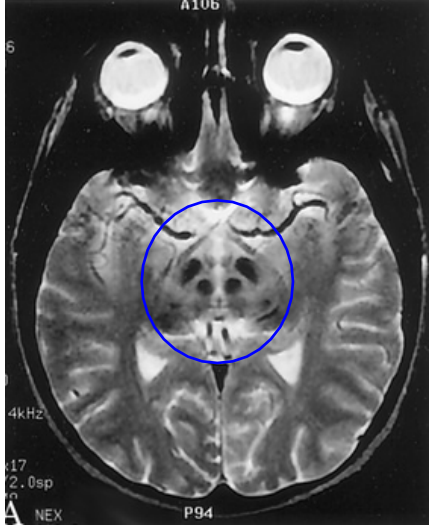
From : Brunet As et Guillaud O, J Hepatol, 2017

- Biology
  - AST > ALT
  - Ceruloplasmin <0,2 g/L
  - Hemolysis
  - Exangeable cupper > total cupper
  - REC > 15%
  - Urinary/Liver cupper

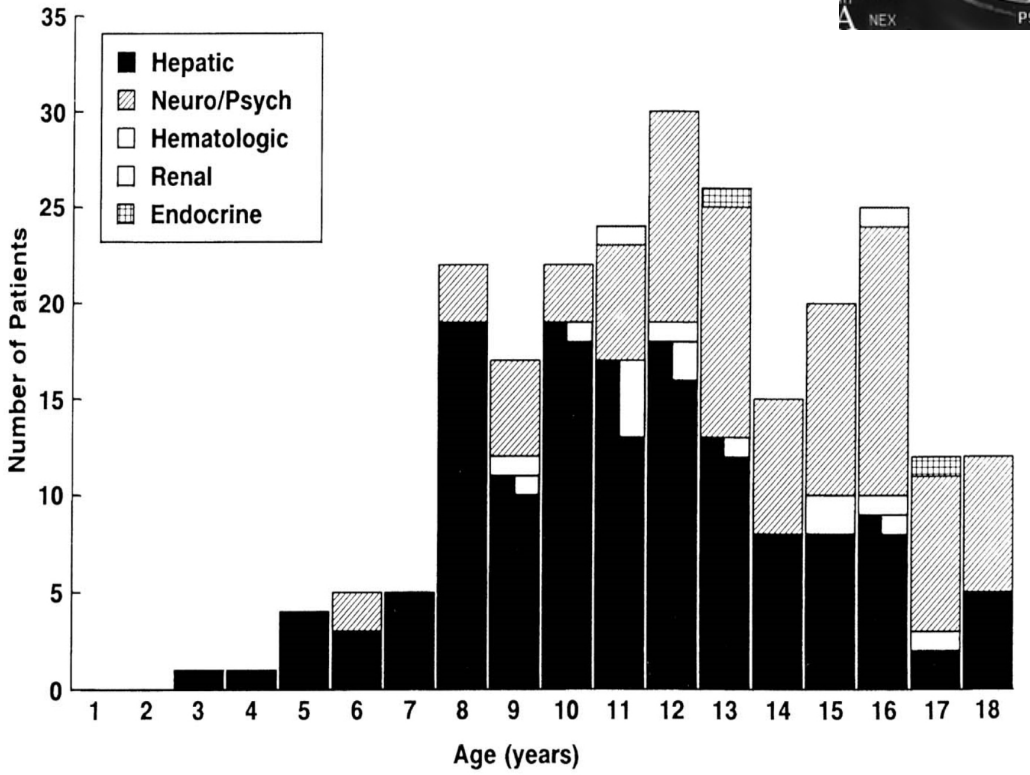


Genetic 1/2 - Wilson Disease





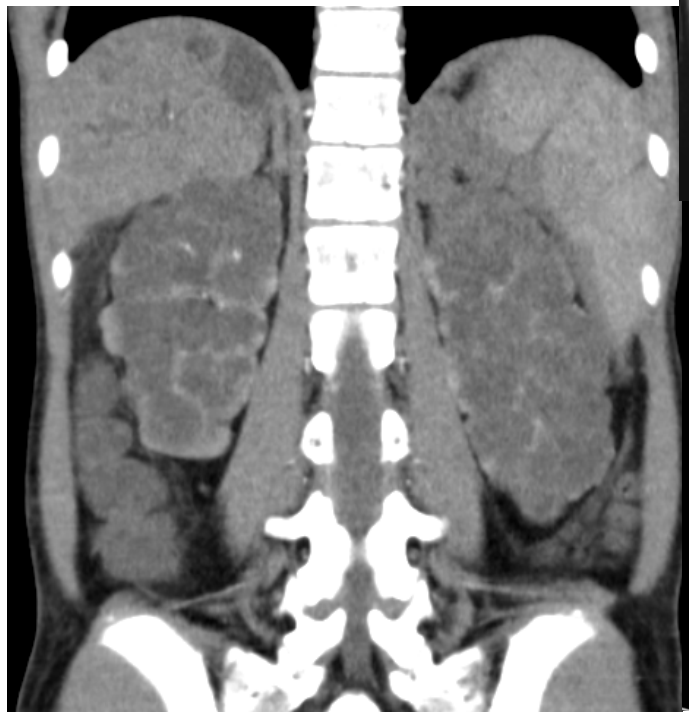
- Cupper accumulation in organs
  - Liver – eye - brain – erythrocytes
- Treatment
  - Low cupper diet
  - **Cupper chelator**
  - Inhibitor of cupper absorption (Zn)
  - Liver transplantation



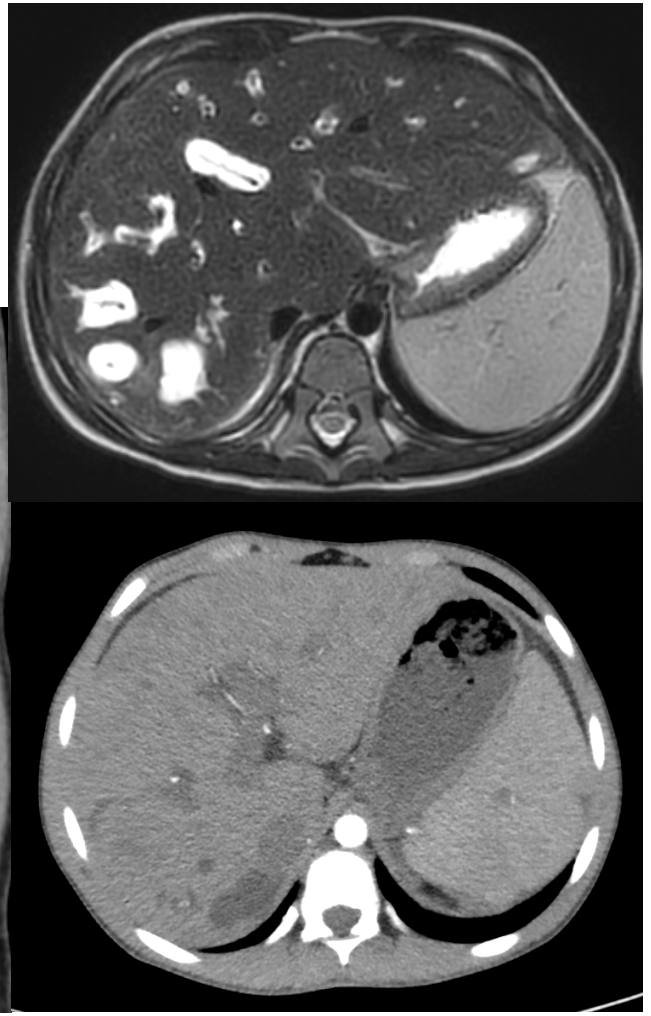
From : Sokol RJ, Copper and Iron disorder, Livers disease in Children, 2001, Zagami AS et al. Neurology. 2001 Mar 13;56(5):665

Genetic 2/2 – Liver/Kidney Polykystosis

- Diagnosis
  - Suspected : imagery
  - Confirmed : PKHD1 mutation++ (recessive)
- Renal impairment at front
  - Portal hypertension
  - Cholangitis
- Treatment
  - Transplantation



TDM



MRI

Vascular

- Portal thrombosis
  - Portal cavernoma
  - Portal hypertension+++
- Budd-chiari
  - Rare (warning postLT)
  - Sus hepatic interruption of venous flux
  - Thrombosis or obstruction vs external compression
- Veino occlusive disease
  - Sinusoidal obstruction
  - Acute : jaundice, ascitis, hepatomegaly
  - History of BMT

- Radiology
  - Portal thrombosis
    - Diagnostic :
      - US : cavernoma, portal hypertension
      - Angio TDM
      - Pressions evaluation
    - Therapeutic : vascular repermeabilisation, radiologic derivation…
  - Budd Chiari
    - US : no sus hepatic flux, demodulated
    - Angio TDM or MRI if doubt

Thank you