Neonatal hyperbilirubinaemia

UNCONJUGATED HYPERBILIRUBINAEMIA

Physiological jaundice

- As hepatic bilirubin glucuronosyl transferase activity is low at the time of birth , nearly all newborn babies have hyperbilirubinemia in the first week of life
- • **Serum bilirubin < 200 μmol/l**
- • **36 > hours, < 2 weeks**
- • **Conjugated bilirubin < 20% of total bilirubin**

UNCONJUGATED HYPERBILIRUBINAEMIA

Physiological jaundice

Factors associated with severe jaundice: breast-feeding, weight loss (> 7 %), maternal diabetes mellitus, bruising, induction of labour with oxytocin, prematurely born infants, genetic control of bilirubin, shortened red blood cell lifespan, increased activity of enterohepatic circulation and inefficient uptake of bilirubin by hepatocytes

Physiological jaundice

Treatment

Treatment may not be necessary in most cases. Phototherapy should be iniciated only when serum total bilirubin > 300 μmol/l in term infants

(> 200 μmol/l in premature babies)

UNCONJUGATED HYPERBILIRUBINAEMIA

- **Breast-milk jaundice**

- Moderately severe unconjugated hyperbilirubinaemia associated with breast-feeding is common, occurring in 0.5-2% of healthy newborn babies.
- • After the fourth day (late pattern)
- • Towards the end of the first week (late pattern) and usually peaks around the end of the first week

UNCONJUGATED HYPERBILIRUBINAEMIA

- **Breast-milk jaundice**

- The aetiology remains uncertain
- • Contamination of breast-milk with steroids such as pregnandiols appears unlikely
- • Breast milk contain fatty acids which displace in the intestinal content and enhance the enterohepatic circulation of bilirubin
- • Breast milk contain β-glucuronoidase, leading to deconjugation of glucuronide moieties from conjugated bilirubin and subsequent resorption of bilirubin
- • Breast- fed babies have less frequent stools and eliminate less bile in feces than bottle fed babies

UNCONJUGATED HYPERBILIRUBINAEMIA

- **Breast-milk jaundice**

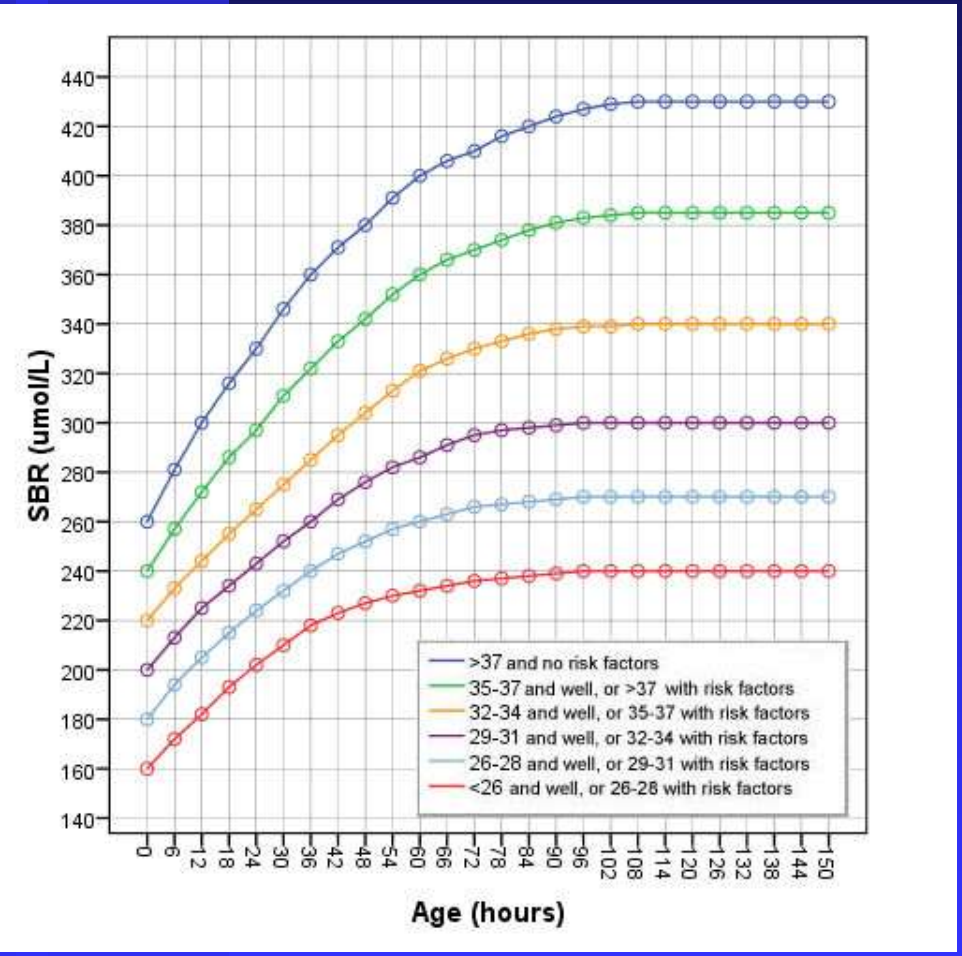
- ***Diagnosis*** is clinical : exclusively breast-fed baby with unconjugated hyperbilirubinemia, normal conjugated bilirubin, haemoglobin and reticulocyte counts, no maternal blood group incompatibility and a normal physical examination except for jaundice
- The diagnosis is supported by a drop in serum bilirubin ($\geq$50% in 1-3 days) if breast-feeding is interrupted for 48 hours.
- Breast –milk jaundice lasting 1-2 months requires surveillance to exclude liver disease.

UNCONJUGATED HYPERBILIRUBINAEMIA

- **Systemic disease**

- Haemolysis of any aetiology (Rh and ABO incompatibility, glucose-6-phosphate dehydrogenase deficiency, erythocyte membrane defects, and spherocytosis).
- Bruising
- Haemorhage into brain or lung tissue,
- Neonatal polycythaemia
- Congenital hypothyreoidism
- Sepsis
- Hypoxia
- Hypoglycaemia
- Galactosaemia
- Fructose intolerance

UNCONJUGATED HYPERBILIRUBINAEMIA



- Neonatal hyperbilirubinaemia charts

UNCONJUGATED HYPERBILIRUBINAEMIA

Systemic disease

Inherited disorders

Crigler-Najjar syndromes

- are autosomal recessive conditions which lead to unconjugated hyperbilirubinaemia due to deficiency of the enzyme bilirubin uridine diphosphate glucuronosyl transferase (UDPGT). In type 1 there is effectively no UDPGT] present, in type 2 the defect is partial.

- Type 1 is much more severe (bilirubin 250-850 μmol/l) than type 2 (200-300 μmol/l) and may be reduced by 40% when phenobarbitone is administered
- Crigler-Najjar syndrome type 1 Phototherapy , liver transplantation
- Crigler-Najjar syndrome type 2 – phenobarbitone (5-10 mg/kg/day)

UNCONJUGATED HYPERBILIRUBINAEMIA

Systemic disease

Inherited disorders

Gilbert's syndrome

Mild variable unconjugated hyperbilirubinaemia

Total serum bilirubin 30-90 μmol/l

Gene defect

There is a mild jaundice which is exacerebated by dehydratation, intercurrent illness or fatigue

More common in males

Serum aminoransferases are normal and liver biopsy is unnecessary

Infants homozygous for the genetic abnormality of Gilbert's syndrome have greater increase in jaundice in the first two days.

Treatment is not required

Cholestatic jaundice
CONJUGATED HYPERBILIRUBINAEMIA

- Cholestatic jaundice in infancy affects approximately 1 in every 2500 term infants and is infrequently recognized by primary providers in the setting of physiologic jaundice.
- **Cholestatic jaundice is always pathologic and indicates hepatobiliary dysfunction.**
- The most common causes of cholestatic jaundice in the first months of life are **biliary atresia (**25%–40%) followed by an expanding list of monogenic disorders (25%), along with many unknown or multifactorial (eg, parenteral nutrition-related) causes, each o which may have time-sensitive and distinct treatment plans.

CONJUGATED HYPERBILIRUBINAEMIA

- Conjugated hyperbilirubinaemia nearly always indicates liver disease, which may be due to the neonatal hepatitis, syndrome, biliary atresia, or duct paucity syndromes.
- Neonatal hepatitis syndrome is now the term given to nonspecific hepatic inflammation which develops secondary to many different aetiologies, including intrauterine infection, endocrine disorders and inborn errors of metabolism

CONJUGATED HYPERBILIRUBINAEMIA

- Any infant noted to be jaundiced after 2 weeks of age be evaluated for cholestasis with measurement of total and direct serum bilirubin
  - **Neonatal cholestasis –**

conjugated (direct) bilirubin > 34 umol/l
or direct bilirubin > 20% of total bilirubin in the first two months of life!

CONJUGATED HYPERBILIRUBINAEMIA

- **Infections**

- ***Toxoplasmosis, rubella, cytomegalovirus, herpes simplex (TORCH) infections, syphilis, varicella***
- Cytomegalovirus (CMV) the most common congenital infection, affects 1% to 2% of newborns. Most infected newborns are asymptomatic.
  - Unfortunately 5% to 10% of the patients have a myriad of clinical symptoms that include low birth weight, microcephaly, periventricular calcifications, chorioretinitis, and deafness.
  - Hepatosplenomegaly and direct hyperbilirubinemia are the most prominent liver-related problems.
  - The diagnosis of congenital CMV is confirmed by culture or PCR from the nasopharynx, saliva, blood, or urine soon after birth. Urine CMV culture or CMV-DNA

CONJUGATED HYPERBILIRUBINAEMIA

- **Infections**

- ***Hepatotropic viruses: hepatitis A, B and C***
- ***Hepatitis A*** is rare in the neonate, but congenital infection may occur
- ***Hepatitis B*** vertical transmission is subclinical in the neonatal period
- Vertical hepatitis B infection
- Pregnant women HbsAg+ 0.6%
- Pregnant women HbsAg+, HbeAg+ : 90-95% risk
- Pregnant women HbsAg+, HbeAg- : 15-20% risk
- **Immunoprophylaxis**
- ***Hepatitis C*** is not a cause of neonatal hepatitis

- In general, these hepatotropic viruses do not cause neonatal cholestasis.

CONJUGATED HYPERBILIRUBINAEMIA

- **Infections**

- *HIV infection*
- *Parvovirus B19 infection*
- *Human herpesvirus-6 (HHV-6) infection*
- *Syncytial giant/cell hepatitis (paramyxovirus infection)*
- *Enteric viral sepsis (echovirus, Coxsackie viruses, adenoviruses)*
- *Bacterial infections outside the liver(/urinary infections)*
- *Listeriosis*
- *Tuberculosis*

CONJUGATED HYPERBILIRUBINAEMIA

Endocrine disorders

- ***Hypothyreoidism***
  - The newborn screen is designed to detect high levels of thyroidstimulating hormone (TSH); hence, in cases of central hypothyroidism, this can be missed and repeating a blood TSH, free T4, and T3 may be helpful
- ***Panypopituitarism***
  - Pituitary hormones are involved in the regulation of bile synthesis and excretion and bile flow.

Chromosomal disorders

- ***Trisomy 18***
- ***Trisomy 21***
- ***Cat-eye syndrome***

CONJUGATED HYPERBILIRUBINAEMIA

Toxic injury

Total parenteral nutrition associated cholestasis

Drug-induced hepatotoxicity

Idiopathic neonatal hepatitis

In up 25% of infants presenting with conjugated hyperbilirubinaemia before 3 months of age, no aethiology is found.

CONJUGATED HYPERBILIRUBINAEMIA

METABOLIC DISEASES

α1-antitrypsin deficiency

- This autosomal recessive condition is the most common cause of inherited neonatal cholestasis.
- Approximately 10% to 15% of neonates with this condition will present with cholestasis and a combined picture of hepatocellular injury and obstruction with elevation of the ALT, AST, GGT, and AP.
- The cholestasis is usually severe and the presence of acholic stools may present a challenge because of the resemblance to biliary atresia. Although some patients may develop cirrhosis early on,jaundice clears in most patients by 4 months of age

CONJUGATED HYPERBILIRUBINAEMIA

METABOLIC DISEASES

α1-antitrypsin deficiency

- Deficiency occurs in 1 in 1600-2000 live birth
- The primary biological function is to bind and inactivate leucocyte elastase
- Pi phenotype system, more than 75 variants
- Pathogenesis of liver disease is unknown

CONJUGATED HYPERBILIRUBINAEMIA

- **METABOLIC DISEASES**
- **α1-antitrypsin deficiency**

- The diagnosis is made based on the phenotype (normal: MM; abnormal: ZZ or SZ; heterozygous: MZ, MS)
- Checking for serum levels of a-1-antitrypsin ((normal > 1.0 g/l) could be helpful if used along with the phenotype to distinguish patients who are homozygous for the Z allele or SZ compound heterozygotes, both of whom may develop liver disease.
- Serum a- 1-antitrypsin concentrations alone are an insufficient test since a-1- antitrypsin is an acute phase reactant and during illnesses may be .
- Antenatal diagnosis is now available

CONJUGATED HYPERBILIRUBINAEMIA

METABOLIC DISEASES

α1-antitrypsin deficiency

Prognosis:

- Approximately half do well; of these infants ,half are entirely normal and the other half have mildly abnormal serum aminotransferases but no progression of liver disease.
- The other half do poorly; half develop persisting cholestasis with progressive hepatic decompensation and may die or require liver transplantation in the first year of life.
- In the other half, jaundice resolves, but serum amoinotransferases are abnormal. The infants develop cirrhosis with eventual hepatic insufficiency

CONJUGATED HYPERBILIRUBINAEMIA

METABOLIC DISEASES

- Cystic fibrosis
- Primary disorders of bile acid synthesis
- Tyrosinaemia
- Galactosaemia
- Hereditary fructosaemia
- Glycogen storage disease , type IV
- Niemann-Pick, type A
- Niemann Pick , type C
- Wolman disease

CONJUGATED HYPERBILIRUBINAEMIA

STRUCTURAL ABNORMALITIES

Extrahepatic biliry atresia (EHBA)

- EHBA is a cause of liver disease in 25% - 40% of infants presenting with neonatal hepatitis syndrome and is the most important differential diagnosis.
- Incidence 1 in 8000-15 000 live birth.
- The etiology of EHBA is unknown and theories of pathogenesis include genetic contributions to bile duct dysmorphogenesis, viral infection, toxins, chronic inflammatory or autoimmune-mediated bile duct injury

STRUCTURAL ABNORMALITIES
Extrahepatic biliry atresia (EHBA)

- There are 3 classifications of EHBA:

1. **the nonsyndromic form** (84%), which is the most common;
2. **EHBA with at least 1 malformation but without laterality** (eg, situs inversus) defects (6%)
3. **the syndromic EHBA with laterality defects (10%).**

- The latter 2 groups have other associated anomalies predominantly in the cardiovascular (16%) and gastrointestinal (14%) systems, but the group without laterality defects has more frequent genitourinary
- anomalies. Patients with BA with laterality defects more commonly have splenic anomalies

CONJUGATED HYPERBILIRUBINAEMIA

STRUCTURAL ABNORMALITIES

Extrahepatic biliry atresia (EHBA)

Clinical features

- Normal birth weight and gestational age in the majority. Preterm infants can have EHBA
- Jaundice, which is present shortly after birth, continuous with physiological jaundice. There may be some variability,however, jaundice can be readily identified in affected infants by 4 weeks of age.
- Yellow or dark urine with increasingly pale stools, which eventually become acholic.
- Hepatomegaly, liver is usually firm
- Splenomegaly is late sign
- Failure to thrive
- Cardiovascular anomalies (ventricular or atrial septal defects) in 30 %
- Polysplenia syndrome, this includes preduodenal portal vein, situs inversus, absence of inferior vena cava and malrotation
- Bleeding from vitamin K-responsive coagulopathy
- Ascites and pruritus

CONJUGATED HYPERBILIRUBINAEMIA

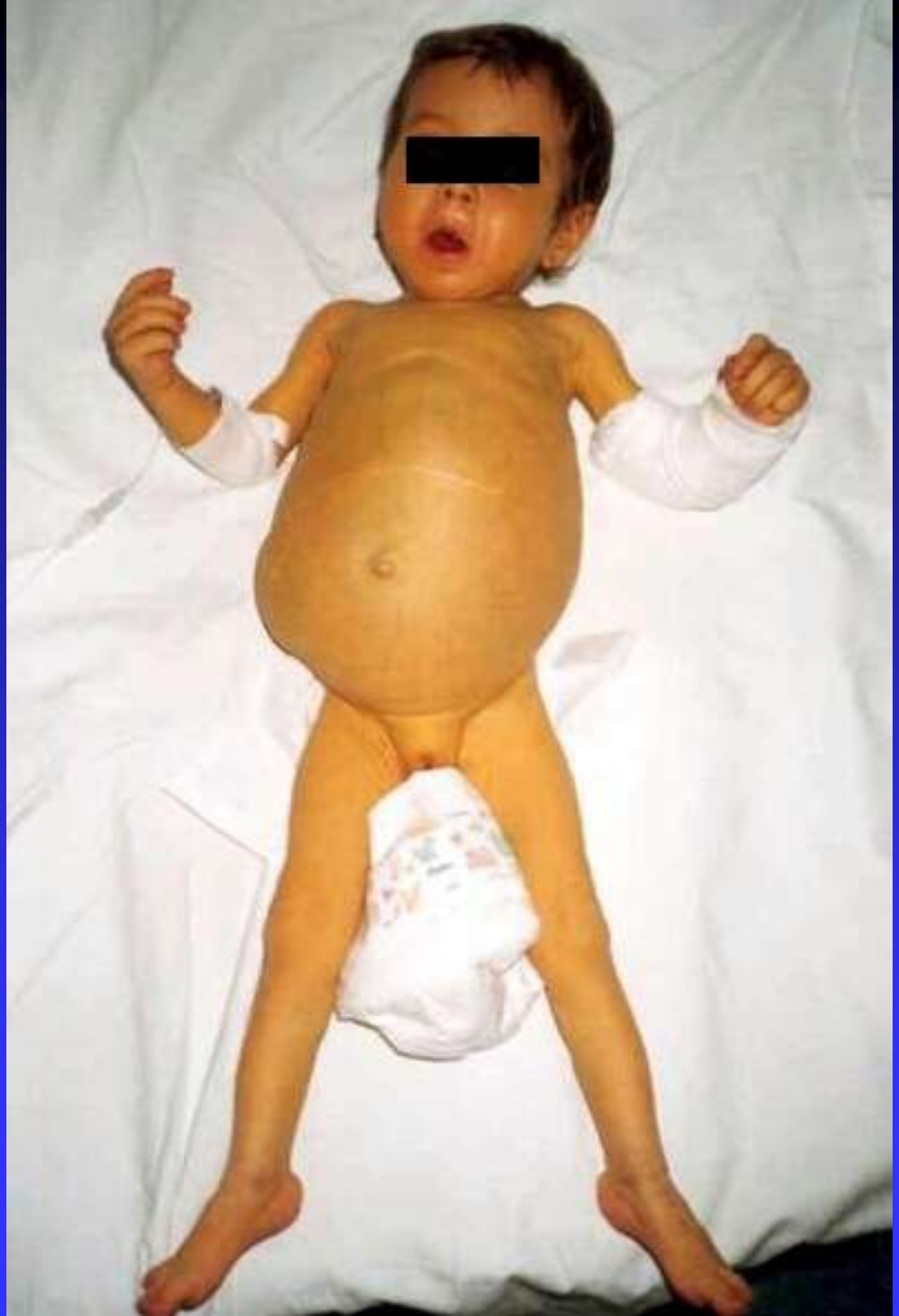
STRUCTURAL ABNORMALITIES

Extrahepatic biliry atresia (EHBA)

Diagnosis

- Serum conjugated bilirubin (40- 200 μmol/l)
- Elevated aminotransferases, GGT, ALP
- Serum albumin is usually normal
- Cholesterol may be elevated but triglycerides are normal
- Protrombin time is normal, although 5-10 % of cases present vitamin K-responsive coagulopathy
- Hepatic ultrasound
- Hepatobiliry scanning
- Percutaneous liver biopsy
- Endoscopic retrograde cholangiography

Optimally, the diagnosis of EHBA must be established before the infant is 5-7 weeks old so that Kasai portoenterostomy can be performed by 6-8 weeks of age.



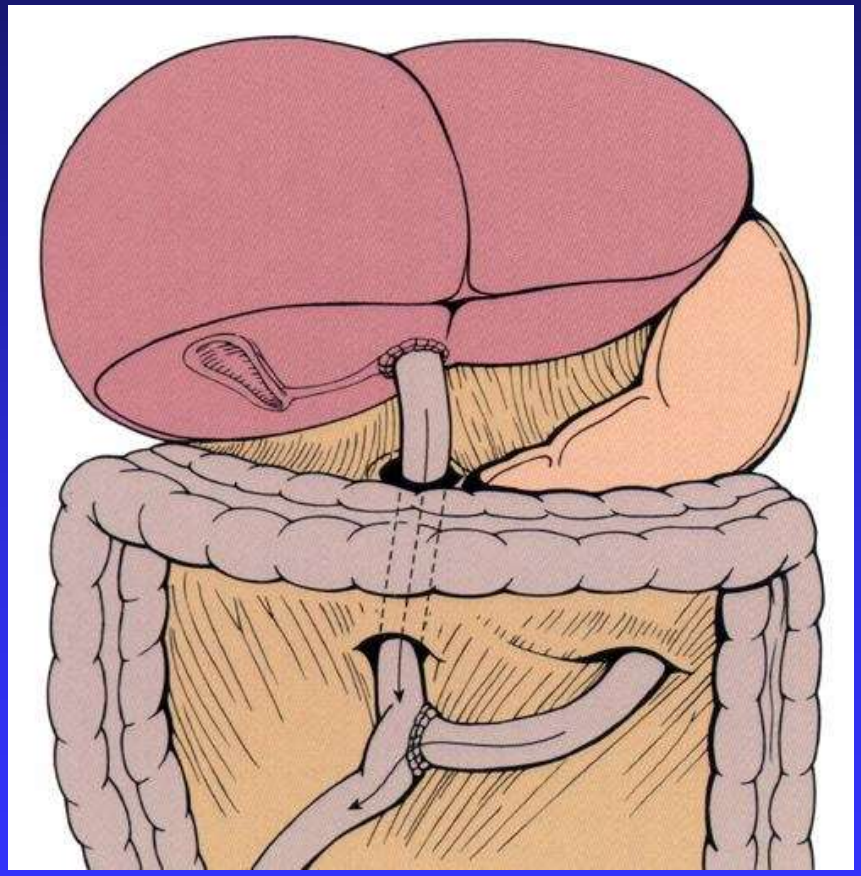
Biliary atresia

Pale stool

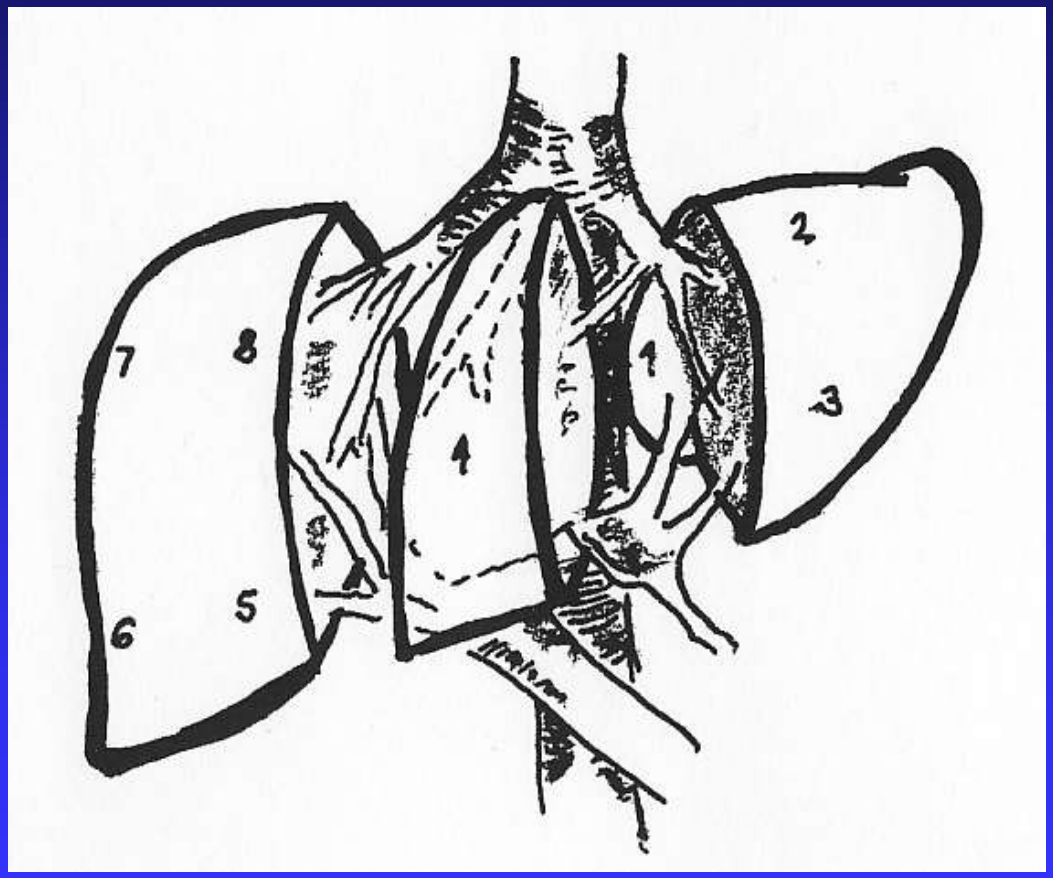
Hepatoportoenterostomy (Kasai procedure)

- Prognosis of this condition/procedure comprises the following:
- If performed before 60 days of age, 80% of children achieve some bile drainage
- Prognosis is progressively worse the later surgery is done
- Post-operatively, **cholangitis** **and** **malabsorption** are common
- Many children with biliary atresia will require **liver transplantation** **(75 %)** despite the attempted surgical repair, although on occasion, it can be delayed until adulthood.

Hepatoportoenterostomy (Kasai procedure)

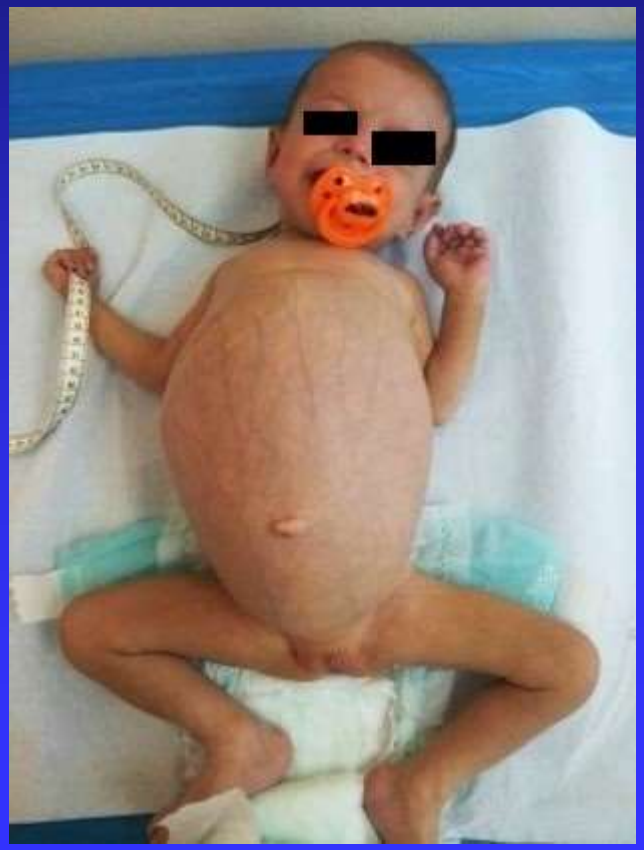


Extrahepatic biliry atresia liver transplantation



Liver transplantation

Long-term survival after 10 years is 85-93%



CONJUGATED HYPERBILIRUBINAEMIA

STRUCTURAL ABNORMALITIES

- **Choledochal cysts**
- **Alagille syndrome**
- **Cystic fibrosis**
- **Bile duct paucity syndromes**
- **Nonsyndromatic duct paucity**

Alagille syndrome

- Clinical criteria for the diagnosis of ALGS includes ductopenia on liver biopsy and a characteristic Alagille facies (**broad forehead, small pointy chin, but is often difficult to recognize in the neonatal period), posterior embryotoxon, butterfly vertebrae, renal disease, and a variety of developmental cardiac defects (most commonly peripheral pulmonic stenosis) or tetralogy of Fallot.**

CONJUGATED HYPERBILIRUBINAEMIA

STRUCTURAL ABNORMALITIES

Progressive familial cholestasis (PFIC)

- Different types of progressive familial intrahepatic cholestasis (PFIC) syndromes associated with low or high GGT phenotype have been characterized.
  - Byler disease (PFIC I) **neonatal hepatitis, pancreatic insuficiency and malabsorption,** GGT normal serum levels, chromosome 18,(q21-q22), bile coarse granular appearence
  - PFIC 2, (BSEP protein deficiency), GGT normal serum levels, bile is amorphous, chromosome 2q24, Isolated defect in bile acid transport. **Hepatitis with giant hepatocytes, fibrosis, pruritus**
  - PFIC 3 with high GGT - MDR deficiency. MDR3 gene product plays role in excretion of major lipid component in bile.
  - Benign recurent intrahepatic cholestasis (BRIC), a rare genetic disorder characterized by **recurrent** episodes of **cholestatic** jaundice. It is a **benign** disease and even after repeated episodes (GGT normal serum levels)