BILIARY ATRESIA

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Abstract

Extrahepatic biliary atresia (EHBA) is an inflammatory fibrosing process affecting the extrahepatic and intrahepatic biliary tree resulting in fibrous obliteration of the extrahepatic biliary tract, ductopenia of intrahepatic bile ducts, and biliary cirrhosis. EHBA is divided in a fetal, prenatal or embryonic, and a more common, perinatal form. The symptoms of the fetal form start shortly after birth and there is frequently an association with a variety of congenital anomalies. Children with the perinatal form become jaundiced several weeks after birth; no associated congenital anomalies are present. Morphologically, an inflammatory and fibrosing process of the extrahepatic biliary tree leads to complete luminal obliteration. The liver is characterized by a nonspecific giant cell transformation, and portal expansion by fibrous connective tissue with marked ductular proliferation. The differential diagnosis with other conditions with similar microscopic patterns such as alpha-1 antitrypsin deficiency, total parental nutrition, obstruction by a choledochal cyst, arteriohepatic dysplasia, familial progressive intrahepatic cholestasis a. s. o. is discussed. Different etiologies have been postulated in the perinatal form of EHBA: genetic susceptibility, vascular factors, toxins, and infections. EHBA is a heterogenous disease, resulting from a combination of genetic factors, insults, and immunologic pathways. The treatment of EHBA is surgical, whit anastomosis between the biliary tree and the intestine in the "correctable" type and a hepatic portoenterostomy (HPE) for "noncorrectable" group. HPE is a temporizing treatment allowing the infant to develop and grow, followed in the majority of the patients by liver transplantation.

Key words: cholestasis, conjugated hyperbilirubinemia, extrahepatic biliary atresia, and pediatric diseases of the liver.

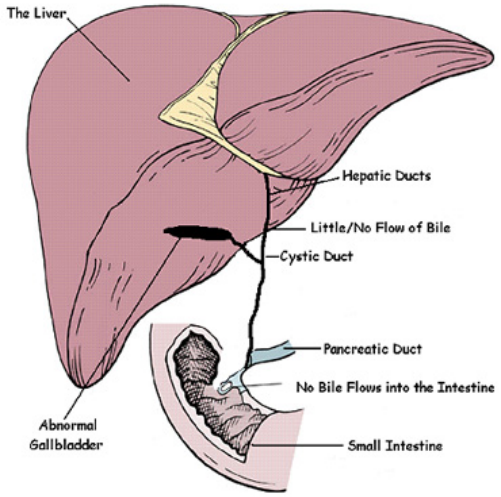
INTRODUCTION

EHBA is defined as a complete fibrous obliteration of a portion or of entire extrahepatic biliary tree, not associated with calculi, neoplasm or rupture (fig. 1). This process is dynamic, inflammatory and fibrosing and involves the extra- and intrahepatic biliary tree and leads to obliteration of the extrahepatic biliary tree, biliary cirrhosis and ductopenia.

HISTORY

J. Burke made the first description of the disease in 1817. In 1916 Holmes introduced in a review the concept of correctable and noncorrectable types of disease. Ladd reported the first successful surgery for the correctable type in 1928. In 1953, Gross documented that extrahepatic biliary atresia was the most common condition causing obstructive jaundice in the first month of life, and that most patients had he noncorrectable type of disease. In 1957, Kasai et al introduced HPE for surgical treatment of biliary obstruction in infants considered to have noncorrectable biliary atresia. (2) Increased experience with hepatic portoenterostomy has revealed that the intrahepatic component of ductal pathology is of great importance in determining prognosis. Liver transplantation was presented by Starzl et al in 1963 as optional therapy for patients in whom hepatic portoenterostomy was unsuccessful. (3)

Fig 1: the disease (1)



EMBRYOLOGY

The liver and biliary tree develops inseparably. The hepatic bud is an endodermal diverticulum that arises late during the third embryonic week from the ventral portion of the foregut, in the section corresponding to the duodenum. This diverticulum has a caudal and a cranial portion. The cranial portion develops into liver, with intrahepatic bile ducts and a portion of the hepatic ducts, including these ducts cholangiocytes. The caudal potion becomes bile duct, cystic duct, and gallbladder.

The epithelium of the cranial portion of the hepatic bud grows into the mesenchyme of the septum transversum. This mesenchyme appears necessary for the induction of hepatocyte differentiation. The liver-committed epithelium cloaks vessels of the vitelline venous plexus; blood leaving the developing liver drains into the sinus venosus. As the embryo lengthens, the duodenum no longer is apposed to the septum transversum, so that the ventral mesentery (the lesser omentum) comes to contain the extended stalk derived from

the caudal hepatic bud. (4,5) This is the anlage of extrahepatic bile ducts.

Within the embryonic liver, portal tracts are defined by condensations of mesenchyme around vessels. Hepatoblasts are a cell type capable of differentiation into either hepatocyte or cholangiocyte, at the margin of these tracts, constitute the ductal plate. This becomes apparent between the 9th and 10th embryonic week as a layer of cells; this layer is then duplicated focally and by the 12th embryonic week begins to develop lumina. Regression of portions without lumina and outward growth of mesenchyme bring the persistent portions within the portal tract. This process moves outward along the portal tracts as the liver grows, establishing an anastomosing network through which bile can drain toward the hilum. (6,7)

BILIRUBIN PHYSIOLOGY

Newborns are at increased propensity for developing hyperbilirubinemia due to the following physiological handicaps leading to either increased bilirubin production or its decreased excretion.

Increased production

- Newborns have a greater red cell (RBC) mass per kg as compared to that in adults; so they produce 6-10 mg of bilirubin/kg/day as opposed to the production of 3-4 mg/kg/day in adults.
- Newborns have a shorter life span of RBC (80-90 day as compared to120 day in adults).

Decreased excretion

- Defective uptake of bilirubin due to hepatic immaturity and decreased ligandin.
- Defective conjugation due to decreased UDPG-T activity (Uridine diphospho glucuronyl transferaze activity).
- Decreased hepatic excretion of bilirubin.
- Increased entero-hepatic circulation due to higher levels of beta-glucuronidase enzymes in neonatal gut and decreased intestinal bacteria.

METABOLISM OF BILIRUBIN – see table 1 and table 2

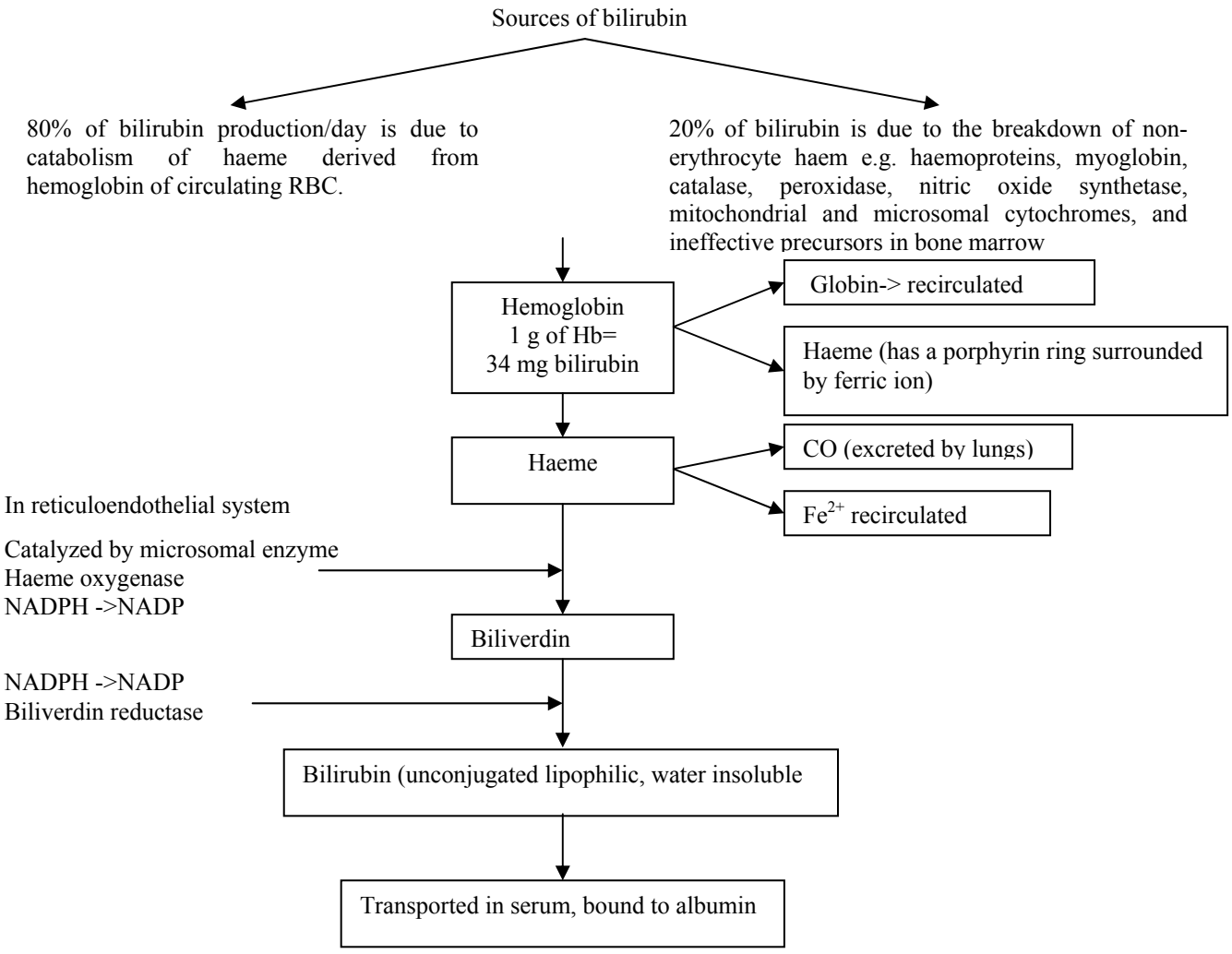


Table 1

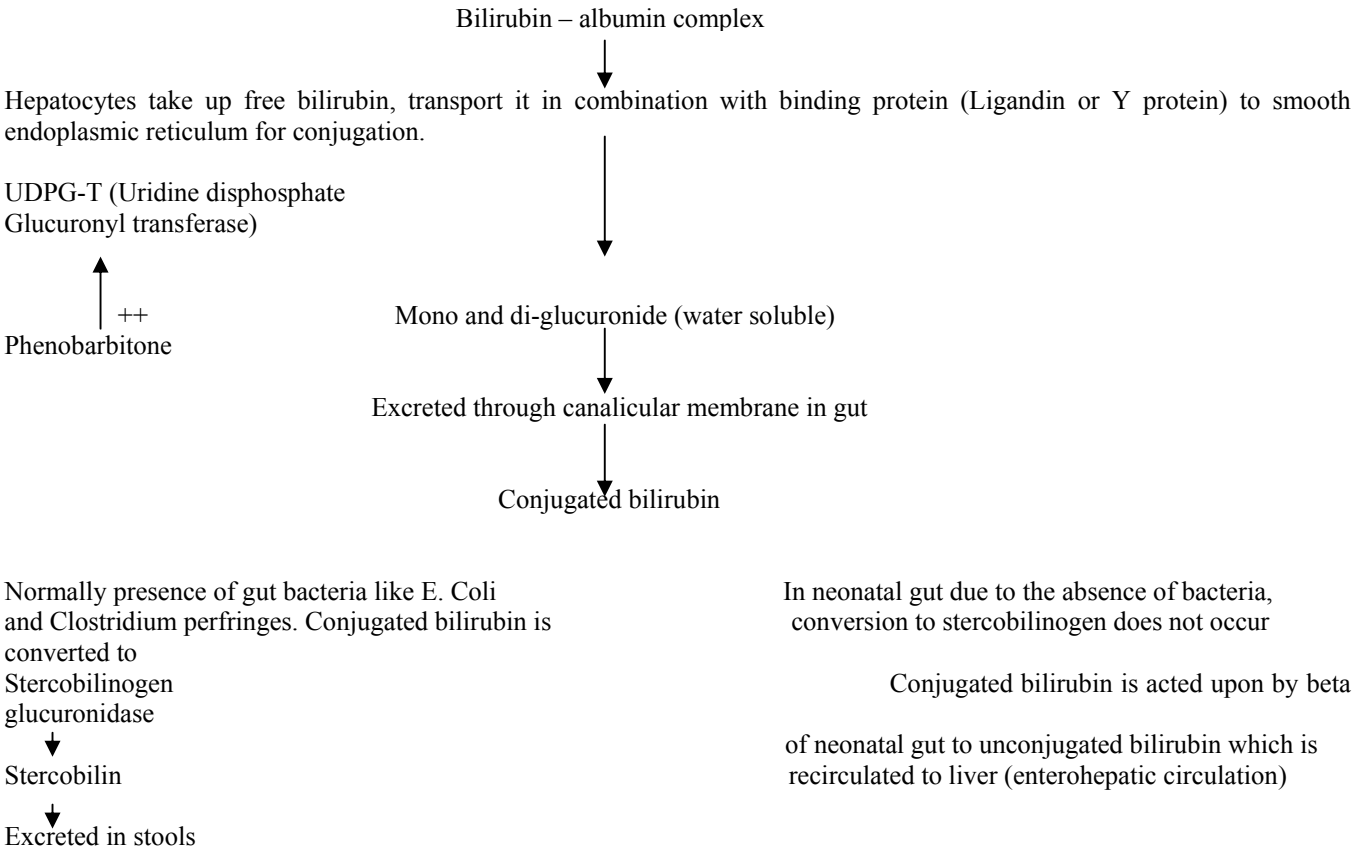


Table 2

FETAL BILIRUBIN METABOLISM

Most of unconjugated bilirubin formed by fetus is cleared by placenta into maternal circulation. Conjugation of bilirubin is limited in fetus due to the decreased hepatic blood flow and the decreased uridine diphosphoglucuronyl transferase (UDPGT) activity. Bilirubin is normally present in amniotic fluid by 12 weeks. Increased amniotic fluid bilirubin level is found in hemolytic disease of the newborn and the fetal intestinal obstruction below the bile ducts. (8)

GENERAL CONSIDERATIONS

- A whole or a part of the extrahepatic bile ducts is absolutely atretic in biliary atresia and completely obstructs bile flow.
- The incidence of biliary atresia is about 1 in 8,000 to 12,000 live births.
- Is a moderate predominance of the disease in females (1: 0, 64).
- Mortality/morbidity: the long-term survival rate for infants' with biliary atresia following portoenterostomy was 45-50% at 5 years and 25-35% at 10 years.
- Liver transplantation may be the only option for long-term survival in the majority of patients
- Patients with biliary atresia may be subdivised into 2 distinct clinical forms: (1) those with isolated EHBA (postnatal form), accounting for 65-90% of cases and (2) patients with associated situs inversus or polysplenia/asplenia with or without other congenital anomalies (fetal/embryonic form), comprising 10-35% of cases.

Table 3: Comparison between fetal and perinatal biliary atresia: incidence, predisposing factors, associations and time of presentation

EHBA type	**Incidence**	**Insult**	**Congenital anomalies**	**Onset**
Fetal	10-25%	Antenatal	Present	Early
Perinatal	Common	Perinatal	Absent	After 2 weeks

Associated anomalies:

- Cardiovascular
- Preduodenal portal vein
- Meckel's Diverticulum
- Malrotation
- Polysplenia
- Asplenia
- Situs Inversus
- Urological
- Pulmonary Hypogenesis
- Umbilical Hernia
- Inguinal hernia
- Others

MORPHOLOGY

The morphologic changes of the extrahepatic tree consist of a spectrum of alteration from epithelial damage of a patent bile duct, to inflammation and fibrosis with obliteration of the lumen, a progressive and dynamic process. The gallbladder is frequently shrunken or atretic. The microscopic changes of the gallbladder and cystic duct are less severe than those of the extrahepatic biliary tree. Similar changes affect the bile ducts of the porta hepatis resulting in several subtypes such as complete fibrous obliteration of the bile ducts, presence of small duct or gland-like structures, and presence of large ducts.

Initial studies of atretic ducts in infant with EHBA grouped the findings into three categories based on the size of the lumen of the bile ducts: type 1 – lumen 150 micrometer or greater; type 2 – ductal structures less than 150 micrometer; type 3 – without epithelium-lined structures, and concluded that presence of bile ducts with a diameter of 150 micrometer or more are correlated with adequate bile flow after surgical intervention and therefore predicts a better outcome. (11) Now, is generally accepted that there is no valid correlation between duct size at time of surgery and prognosis. Absence of bile flow in fibrous remnants has been reported a poor prognostic sign in terms of postoperative bile drainage.

The intrahepatic changes of EHBA at an early stage of disease, before 3 months of age are characterized by nonspecific lobular giant cell transformation with cholestasis, extramedullary hematopoisis, hemosiderin in Kupffer cells), and diagnostic portal changes. All portal spaces are expanded by fibrosis, contain an apparently increased number of interlobular bile ducts, and show marked ductular proliferation. A ductal plate malformation pattern of the ductular proliferation has been observed in patients with a severe form of EHBA. Ductal plate refers to phenotypic changes of periportal hepatocytes characterized by the expression of a biliary phenotype in the cytokeratin stain (CK19 positivity in addition to CK18 expression) around 8-week gestation. These transformed hepatocytes become flattened, form first uni-cell and subsequently double-cell layer that acquires a lumen and extends into the portal space, followed by disruption of the connection to the ductal plate. (11) The cell of the ductal plate will disappear subsequently. This phenomenon of bile duct formation with regression of the ductal plate is called ductal plate remodeling. Bile duct malformation refers to the disturbance in this process with persistence of bile ducts in a ductal plate configuration, numerous dilated bile ducts surrounding a portal space as well as an increase in the number of interlobular bile ducts in the portal space. The ductular proliferation is the typical morphologic presentation of EHBA (a diagnostic biopsy must contain at least five complete portal spaces). (13,14)

After 3 months of age in nonoperated and in most of the operated patients, the portal fibrosis progresses surrounding and subdividing the hepatic lobule, thus resulting in biliary fibrosis and cirrhosis. The number of interlobular bile ducts is considerably reduced by 5 months of age.

Morphologic classification of types of biliary atresia (proposed by the Japanese Society of Pediatric Surgeons)

- Principal types:
  - -type I: atresia of common bile duct
  - -type II: atresia of hepatic duct
  - -type III: atresia of bile duct at the porta hepatis
- Subtypes according to the patterns of distal bile ducts:
  - -a: patent common bile duct
  - -b: fibrous common bile duct
  - -c: aplasia of common bile duct
  - -d: miscellaneous
- Subtypes according to patterns of hepatic radicles at the porta hepatic:
  - -dilated hepatic radicles
  - -hypoplastic hepatic radicles
  - -bile lake
  - -fibrous hepatic radicles
  - -fibrous mass
  - -aplasia of hepatic radicles

ETIOLOGY

The etiologic factors are different in the fetal and perinatal group.

➢ The fetal group

A defect in a yet undefined gene has been postulated for patients with EHBA with extrahepatic malformation; for those without extrahepatic malformation, an abnormal morphogenesis of the bile ducts seems more likely. Several mutated genes have been considered: inversin gene, Kartagener gene, CFC1, JAG1, and HLA class II gene. (15)

➢ The perinatal form

- a genetic susceptibility of patients with EHBA expressed by a high frequency of HLA-B12, with haplotypes A9-B5, A28-B25, B8, DR3.
- Toxin: bile acids, alcohol, environmental factors
- Vascular: patent ductus arteriosus, hepatic arteriopathy

Infectious: hepatitis C virus, rubella, cytomegalovirus, Epstein-Barr virus, human papilloma virus, reovirus 3, rotavirus. (16,17)

PATHOGENESIS

The pathogenesis of EHBA is controversial. It is a heterogeneous disease, the end result of different causal and

pathogenetic mechanisms operating at different periods of gestational and postnatal development.

- For the fetal type, genetic mutations and ductal plate malformation seem to play a major role. Mutation of the JAG1 gene may lead to malformation or dysfunction of the intrahepatic bile ducts. The defect in remodeling of the ductal plate is a result in an inadequate mesenchymal cuff around the hilar bile ducts. These deficient bile ducts rupture resulting in inflammation and fibrosis and bile duct obliteration at the porta hepatis.
- For the perinatal type, the infection, apoptosis and cell necrosis, inflammation, fibrosis – play a major role.

-infection: no single agent has been identified as causative for biliary atresia, though the role of infecting organisms has been the most extensively studied. CMV, rotavirus, reovirus, common hepatitis A, B, C was studied, but no clear associations have been found. (steroid therapy may modulate the inflammation)

-apoptosis and cell injury. Apoptosis is increased in EHBA. Apoptosis results in cell death activation of caspase protease, and upregulation of Fas ligand (FasL). Injured hepatocytes lead to induction of cytokine expression and subsequent activation of hepatic stellate cells, thus perpetuating inflammation and fibrosis.

Caspase inhibitor constitutes a potential therapeutic modality to interrupt the ongoing bile duct destruction.

-inflammation (high level of serum interferon-inducible protein-10, TNF-alpha correlated with abnormal liver function test results). (18,19)

-fibrosis – occurs through activation of macrophages. It was observed elevation of inteleukin-18 (IL-18) in the serum and activation of Kupffer cells.

The antibody therapy against IL-18 may arrest progression of the disease. (19)

Other causes

Disorders of bile acid synthesis are part of the differential diagnosis of EHBA. In fact, bile acids almost certainly contribute to ongoing hepatocellular and bile ductular damage in infant with the disorder. Although associated defects in bile acid metabolism may hasten progression of liver disease, no primary role for bile acids in the development of biliary atresia has been identified.

Table 4: Pathogenesis: factors implicated in the different types of EHBA.

Fetal type	**Perinatal type**
Genetic alteration	Infection
Ductal plate malformation	Apoptosis and cell necrosis
	Inflammation
	Fibrosis

CLINICAL PRESENTATION

- Typical symptoms include variable degrees of jaundice, dark urine, and acholic stools, hepatomegaly.
- Most of biliary atresia, most infants are full-term, though a higher incidence of low birth weight may exist; they manifest normal growth and weight gain during the few weeks of life.
- In most cases, acholic stools are not noted at birth but develop over the first few weeks of life. Appetite, growth, and weight may be normal.

Physical findings do not identify biliary atresia. No findings are pathognomonic for the disorder.

Jaundice follows neonatal jaundice in perinatal forms, but appears shortly after birth in others. Pathological jaundice should be considered in a patient with hyperbilirubinemia when the conjugated fraction comprised more than about 20% of the total, or greater than 2mg/dl.

Infants with neonatal cholestasis, pose a unique diagnostic challenge of distinguishing between two broad etiologic categories of neonatal hepatitis and extra hepatic biliary obstruction. Early distinction between the two diagnostic categories has important prognostic implications because an appropriate surgical intervention done before 8-10 weeks, significantly improves the outcome of obstructive lesions.

Neonatal cholestasis should be suspected in a child presenting with a history of jaundice at an age of more than 2 weeks with mustard or turmeric colored urine, with or without other associated histories of pale colored stools, maternal or neonatal morbidity.

Meconium color is normal in most patients. The feces in neonatal period usually are yellowish or light yellowish in most of patients.

The liver gradually increases in size and consistency with aging, a characteristic that reflects the duration of bile stasis.

Splenomegaly follows hepatomegaly.

Patients are active; their growth appears normal during the first few months after birth.

Later, anemia, malnutrition, and maldeveloopment result because of malabsorbtion of fat-soluble vitamins; the liver cirrhosis are develops.

Intracranial bleeding caused by vitamin K deficiency is occasionally encountered.

Most patients, who do not undergo surgery, die of hepatic decompensation, esophageal bleeding, or infection.

The 3-year survival rate for children who did not have any drainage procedure was less than 10%. (20)

DIAGNOSIS

Antenatal diagnosis of EHBA is exceptional. EHBA types 1 and 2, witch is rare, can be suspected on antenatal ultrasonography scans when a cystic structure is detected in the liver hilum. Postnatal examination has to distinguish the cystic form of EHBA, which requires urgent surgery, from a choledochal cyst for which surgery may be delayed.

Non-visualization of the foetal gallbladder in early pregnancy (14-16 weeks gestation) may be associated with severe foetal anomalies, including polymalformation syndromes, chromosomal aberrations, cystic fibrosis: amniocentesis is recommended for cystic fibrosis screening, hepatic enzymes tests and chromosomal analysis. Gallbladder may be visualized later in pregnancy, suggesting a delay in its recanalication process. When the gallbladder remains undetectable after birth, the possibility that the patient has EHBA has to be carefully investigated. The incidence of agenesis of the gallbladder (without EHBA) is estimated at approximately 1/6000 pregnancy.

Features of polysplenia syndrome may be detected by antenatal ultrasonography. They may be part of a cardiosplenic syndrome whose prognosis depends mainly on the underlying cardiopathy. Interrupted inferior vena cava may be isolated and benign. Neonates with features of polysplenia syndrome should be carefully followed in order to rule out EHBA.

Postnatal diagnosis

Pathologic jaundice should be considered in a patient with hyperbilirubinemia when the conjugated fraction makes up more than approximately 20% of the total.

Many factors may cause pathologic jaundice in the neonatal period. A series of blood studies can indicate a diagnosis of infection, hematologic problems, metabolic diseases, or genetic disorders (e.g. alpha-1 antitrypsin deficiency).

Neonatal hepatitis and interlobular biliary hypoplasia (paucity of interlobular bile ducts) are most likely to be confused with biliary atresia.

According to Alagille, clinical features and laboratory data allow differentiation between biliary atresia and neonatal hepatitis in 83% of cases before the age of 3 months. (21)

CAUSES OF NEONATAL HYPERBILIRUBINEMIA

Unconjugated hyperbilirubinemia (Table5)

Hemolytic causes
- *Overproduction* – blood group incompatibility: ABO, Rh
- *RBC membrane defects*
  - Hereditary eliptocytosis
  - Hereditary spherocytosis
  - Hereditary spherocytosis
  - Hereditary poikilocytosis
- *RBC enzyme defects*
  - Glucose 6 phosphate deficiency
  - Pyruvate kinase deficiency
- *Haemoglobinopaties*
  - Alpha thalasemia
  - Delta-beta thalasemia
- *Acquired haemolysis*
  - Vit K3, nitrofurantoin, sulphon- amides, antimalarials, sepsis.

Non-hemolytic causes
- *Overproduction*
  - Extravasated blood
  - Cephalhematoma
  - Polycytemia
- *Impaired conjugation*
  - Hypotiroidism
  - Gilbert syndrome
  - Crigler-Najjar syndrome
  - Breast milk jaundice
- *Increased enterohepatic circulation*
  - Pyloric stenosis
  - Intestinal obstruction, ileus

Conjugated hyperbilirubinemia (Table 6)

Obstructive disorders:
1. Tumor or band
2. Rotor and Dubin Johnson syndrome
3. Paucity of intralobular bile ducts (syndromic = Alagile's syndrome or non-syndromic)
4. Choledochal cyst and pseudocholedochal cyst
5. Inspissated bile syndrome
6. Cystic fibrosis
7. Biliary atresia

Non-obstructive disorders:
1. Infective causes: bacterial (syphilis), viral (rubella, CMV, hepatitis, coxsackie, enterovirus), protozoal (toxoplasmosis), idiopatic: Neonatal hepatitis
2. Toxic: Novobiocin; IV hyperalimentation
3. Metabolic defects: galactosemia, alpha 1 antitrypsin deficiency, Tyrosinemia, hereditary fructosemia, hypothyroidism

PHYSIOLOGICAL JAUNDICE

In term babies:

- Appears between 30-72 hours of age
- Maximum intensity by 4^{th}/ 5^{th} day
- Serum bilirubin does not exceed 12 mg%
- Disappears by 7-10 days of age

In preterm babies:

- It appears slightly earlier but not before 24 hours of age
- Maximum intensity is by 5^{th} or 6^{th} day
- Serum bilirubin may go up to 15mg%
- Disappears by 8^{th} – 14^{th} day

Factors who accentuated and prolonged physiological jaundice:

- Immaturity
- Birth asphyxia, acidosis, hypothermia, hypoglycemia
- Drugs like vitamin K, salicylates, sulpha drugs, gentamycin, fructosemide, novobiocin.
- Cephalhematoma and concealed hemorrhage.
- Polycytemia and hypothyroidism
- Intrauterine infections.
- Breast milk jaundice.

Criteria to exclude the diagnosis of physiological jaundice, proposed by Maisels (1981):

- Clinical jaundice in first 24 hours of age.
- Total serum bilirubin concentration increasing by more 5 mg/day.
- Total serum bilirubin exceeds 13 mg% in full term and 15 mg% in preterm.
- Direct serum bilirubin more than 1,5-2 mg%.
- Clinical jaundice persisting more than one week in full term and more than two weeks in preterm.

EVALUATION OF JAUNDICED INFANT

I. History:

1. Time of detailed history is suggestive of probable etiology. The age of onset of jaundice gives an important clue to diagnosis. The appearance of jaundice on first day of life is suggestive for a serious disease process like hemolytic disease of newborn, intrauterine infections (TORCH), Crigler-Najjar syndrome. Between 24-72 hours of age, the jaundice is usually physiological. If the jaundice appears after 72 hours then one should think of causes like sepsis, neonatal hepatitis, extrahepatic biliary atresia, breast milk jaundice, metabolic causes, hypertrofic pyloric stenosis or other causes of intestinal obstruction leading to increased enterohepatic circulation.

2. History of clay coloured stools with dark urine is suggestive of cholestatic jaundice.

3. History of delayed passage meconium, with or without vomiting is suggestive of intestinal obstruction.

4. Family history of jaundice in previous sibling in neonatal period is suggestive of ABO, Rh incompatibility.

5. Presence of vomiting with temperature instability and lethargy is suggestive of sepsis.

6. A family history of jaundice, anemia or early gall bladder disease is suggestive of hereditary hemolytic anemia.

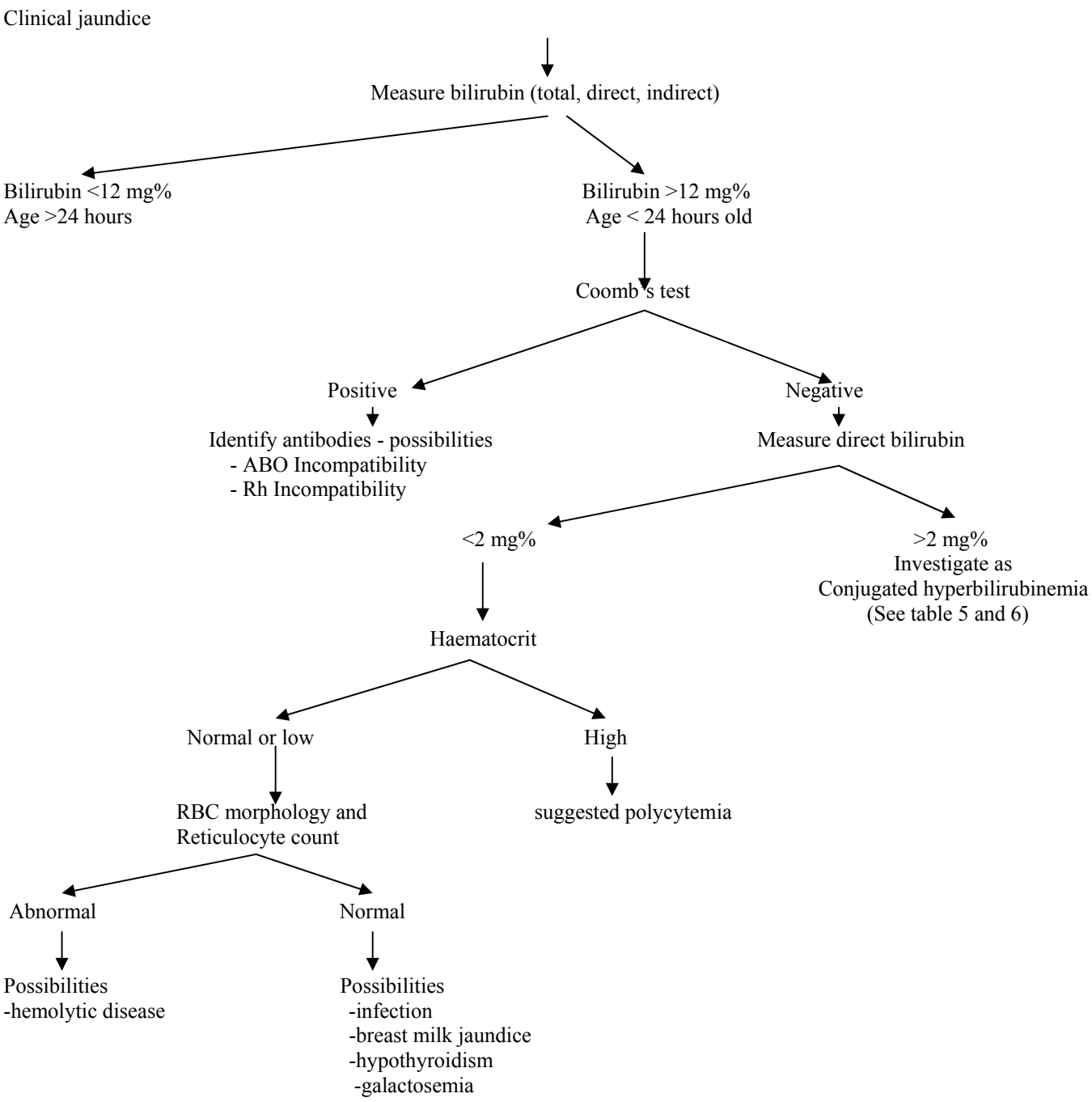
II. Antenatal and obstetric history:

1. antenatal maternal illness may suggested congenital infection (TORCH)
2. maternal diabetes mellitus increased risk of jaundice in infancy
3. maternal drug intake during pregnancy like nitrofurantoin or antimalarials, can lead to hemolysis in G-6 PO4 deficient babies.
4. history of vacuum extraction leads to increased incidence of cephalhaematoma.
5. APGAR score at birth is significant as there are increased chances of neurotoxicity in asphyxiated babies.
6. history of breast feeding might be significant. A distinction should be made between breast milk jaundice in which jaundice is thought to be due to the breast milk itself and breast-feeding jaundice in which low caloric intake may be responsible.

III. Physical examination:

1. jaundice is detected by blanching the skin with finger pressure to observe the color of the skin and subcutaneous tissue in day light. Jaundice progresses in cephalocaudal direction.
2. gestational age and birth weight.
3. microcephaly if is present – may suggested intrauterine infections
4. cephalhaematoma – leads to increased bilirubin load
5. pallor is suggestive for anemia
6. plethora is suggestive for polycytemia
7. petechiae and scratch marks may suggest congenital infections, sepsis, severe hemolytic disease.
8. hepatosplenomegaly – congenital infections, hemolytic anemia
9. umbilical hernia with hoarse cry, large tongue and hypotonia – cretinism.
10. optic fundi if shows chorioretinitis is suggestive for congenital infections.

Table7: Protocol for work up



Laboratory studies for conjugated hyperbilirubinemia:

1. serum bilirubin
2. SGOT, SGPT, alkaline phosphatase, *GPT*, total protein, albumin
3. IgM antibody for TORCH
4. alpha-1 antitrypsin level
5. urine, including determination for reducing substances (for galactosemia)
6. abdominal ultrasound
7. hepatobiliary scan
8. percutaneous needle liver biopsy
9. exploratory laparotomy.

Clinical findings and examination for diagnosis of biliary atresia:

* Routine examination:
  Color of stool
  Consistency of liver
  Conventional liver function tests, including test for gamma-glutamyl transpeptidase
* Special examination:
  Special biochemical studies:
-serum lipoprotein-X
-serum bile acid

Confirmation of patency of extrahepatic bile ducts:
-duodenal fluid aspiration
-ultrasonography
-hepatobiliary scintigraphy
-endoscopic retrograde colangiopancreatography
-laparoscopy
-surgical colangiography
-near-infrared spectroscopy

Needle biopsy of the liver for histopathological studies.

I. Special biochemical studies

- *serum lipoprotein-X:*
  1. -results of tests for Lp-X are positive in all patients with biliary atresia
  2. -results of tests for Lp-X are positive in 20-40% of patients with neonatal hepatitis
  3. -absence of Lp-X in the serum excludes biliary atresia.
- *serum bile acids*:
  -the serum bile acids level increase in infants with cholestatic disease
  -is not useful foe differentiating biliary atresia from other cholestatic disease
  -serum levels of Lp-X greater than 300mg/dl strongly suggest BA.

II.Confirmation of patency of extrahepatic bile ducts

a. *Duodenal fluid aspiration*

Protocol:

-intravenous support with 5% dextrose-saline solution (120 ml/kg/day)

-an 8 Fr polyethylene tube (90 cm long) was placed via the nostril in the third portion of the duodenum; its position was verified by abdominal radiography after instillation of 3-ml solution of soluble radiopaque material through the tube;

-the duodenal fluid was collected by gravity (without suctioning) every 2 hours in assay tube;

-to stimulate biliary flow, 5 ml of a 20% magnesium sulfate solution was introduced into the tube every 4 hours, and the proximal end was closed 15 minutes;

-every 2 hours, the pH of the fluid collected was assessed by a semiquantitative test. If the pH was less than 6,5, an abdominal radiograph was taken to verify the correct distal position of the duodenal tube;

-permeability of the collecting tube was maintained by instilling 5 ml sterile water every 4 hours, alterned with magnesium sulfate.

Results:

-the test was considered bile positive when a yellow biliary fluid was observed, and the test was concluded at this time.

-when no yellow biliary duodenal fluid was observed, the fluid was collected for another 24 hours and, if negative, was reported as such.

-in the majority of the series reported, the sensitivity (the proportion of patients with BA who were identified by bile negative in the fluid aspiration), was around 97%, the positive predictive value was around 92% and the specificity was higher than 90%

Conclusions:

-this test is inexpensive, not highly invasive; trained personnel with few specialized resources may perform it. (22)

b. *Ultrasonography*

-is a rapid, non-invasive, relatively inexpensive investigative method and produces images in real time

-if is performed by a well-trained professional, provides excellent results;

-the characteristic sign in EHBA is "triangular cord" which represents a cone-shaped fibrotic mass cranial to the bifurcation of the portal vein. This sign is a simple, time- saving, highly reliable, and definite tool in diagnosis of EHBA, representing a high positive predictive value.

-in 2003, Hee-Jung Lee et al, from the Departments of Diagnostic Radiology and Pediatric Surgery in Donsang Medical Center in Korea was studied and measured the thickness of the echogenic anterior wall of the right portal vein (EARPV) , and said that the sole criterion for the TC sign was an EARPV thickness of more then 4 mm on a longitudinal scan. (a thickness of 4 mm was chosen as the upper limit for all normal possible structures that could be possible along the anterior aspect of the right portal vein, including the anterior wall of the right portal vein (1mm), anterior wall of the right hepatic artery (1mm), and the common hepatic duct (1-2mm). (23)

-other observation on the ultrasound images (fig. 2) in EHBA was the gallbladder ghost triad: gallbladder length < 1.9 cm, lack of smooth/complete echogenic mucosal lining with indistinct wall and irregular/lobular contour.

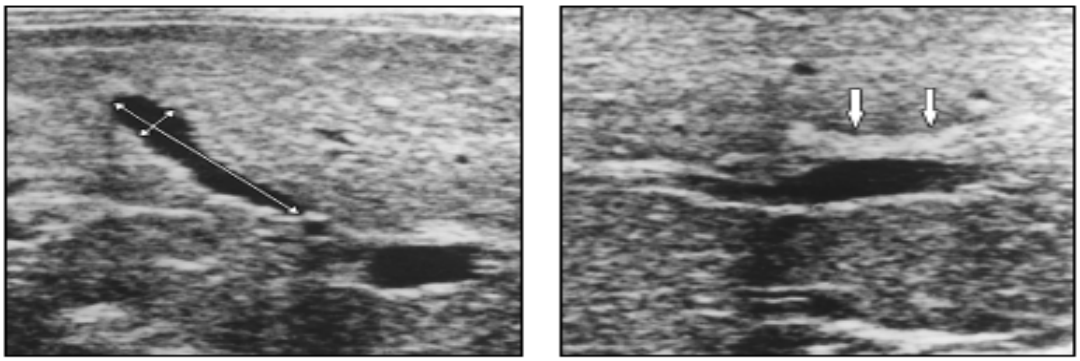


Fig 2: Sonogram illustrates method of measuring gallbladder – images 1, and sonogram reveals tubular echogenic cord – images 2. (24)

-the most frequently used radioisotope is DISIDA Tc99m, which has a very short half-life, low gamma ray emission, very good concentration in the liver, non-conjugated excretion in the bile and a low renal excretion level.

-literature refers to false positive/negative levels of 10%.

-the BRIDA Tc99m isotope is also recommended.

-the DISIDA Tc99m test is not recommended when conjugated bilirubin levels are over 20mg/dl; in such case BRIDA Tc99m should be employed.

-in the normal individuals, the radioisotope is captured by the liver and excreted by the bile ducts to the duodenum.

-the iv administration of the DISIDA Tc99m, should be preceded by the use of Phenobarbital (5mg/kg/day, orally), during 3 to 5 days, aiming at reducing the number of false positive results.

-the immense majority of this test showed the absence of the radioisotope flow to the duodenum, independently on the cause of the cholestasis; the absence of the isotope in the intestine does not indicate with certainty the existence of an extrahepatic biliary obstruction; the presence of the radiotracer in the intestine rule out the hypothesis of EHBA. (25)

c. *Colangiography*

-preoperative colangiography through retrograde laparoscopic or endoscopic via, witch are unavailable in most urban centers, have their use quite limited. After the application of the radiological contrast into the papilla of Vater, we may observe three types of image: (1) bile duct not seen; (2) distal common bile duct and gallbladder seen, no sight of the principal hepatic duct; (3) opacity of the distal common bile duct, gallbladder and principal segment of the hepatic duct, with bile lakes at the porta hepatis.

-colangiography by magnetic resonance imaging.

-operative colangiography, performed after a minilaparotomy, constitutes the last diagnostic method in cases of probable extrahepatic biliary atresia or in those impossible to discard an extrahepatic biliary obstruction.

-in infants with extrahepatic biliary atresia, surgical colangiography is possible to be performed in only 17 to 25% of the cases, due to impossibility of injecting contrast agents through the gallbladder in atresia.

d. *Hepatic biopsy*

-although there are no pathognomonic aspects in the histological analysis of the hepatic material collected by percutaneous or wedge biopsy, the sum of findings provides an important supplement for the formulation of a definitive diagnosis.

-the following were described as findings suggestive of extrahepatic cholestasis: portal duct proliferation, cholestasis in newly formed ducts, pronounced canalicular cholestasis, biliary thrombi in the portal area and accentuated portal and peritubal fibrosis.

-discrete or absent ductile proliferation and the non-existence of portal fibrosis would rule out the possibility of extrahepatic cholestasis

Table 8: Histophatologic differences between idiopathic neonatal hepatitis and extrahepatic biliary obstructions.

Idiopathic neonatal hepatitis	Extrahepatic biliary obstruction
Intracytoplasmic and canalicular cholestasis	Intracytoplasmic and canalicular cholestasis
Disarranged architecture	Preserved architecture
Gigantocellularis transformation	Rare giant cells
Inflammatory infiltrate in the portal space	Discrete inflammatory infiltrate
Little fibrosis	Portal and periportal fibrosis
Extramedullary hematopoisis	**Ductal proliferation**
	Biliary thrombus in the interlobular ducts

DIAGNOSIS CONFIRMED

Once a EHBA diagnosis has been confirmed, the following conduct is indicated: (1) the Kasai portoenterostomy is the first surgical treatment indicated; (2) liver transplantation is indicated in cases of Kasai portoenterostomy failure; (3) the liver transplant should be delayed by as long as possible, with the intention of allowing for maximum patient growth; (4) the liver transplant should not be performed until the occurrence of severe aggravation of the cholestasis, hepatocellular decompensation or severe portal hypertension; (5) multiple attempts to correct an unsuccessful portoenterostomy are not recommended, since the performance of the transplant becomes more difficult and dangerous.

PREOPERATIVE MANAGEMENT

-daily doses of vitamin K (1-2 mg/kg) usually given for several days before surgery;

-prepared the bowel with oral kanamycin in a dose of 50 mg every 8 hours, starting 36 hours before surgery (other authors doesn't recommend the bowel preparation).

-oral feedings are discontinued and saline enemas are given 24 hours before surgery.

-blood is cross-matched and preoperative broad spectrum antibiotics are administred.

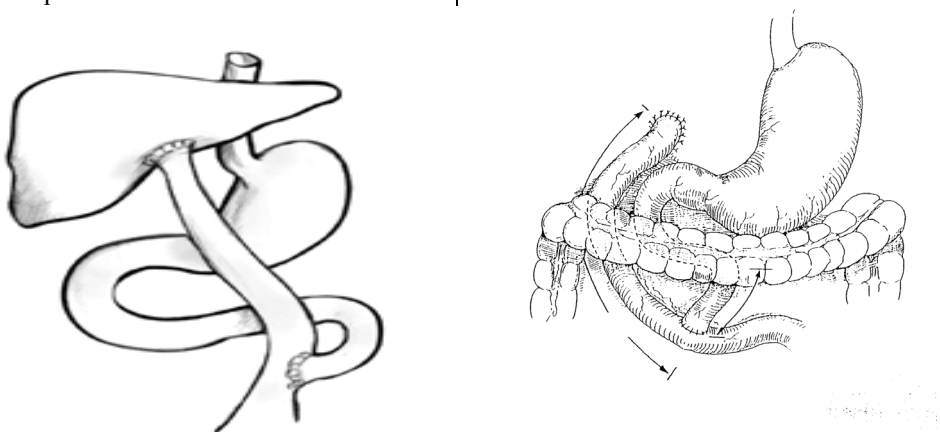
SURGICAL MANAGEMENT

Many technical variants are possible, according to the anatomical pattern of the biliary remnant.

Table 9: Anatomical types of biliary atresia (Bicetre) (1)

French classification	Frequency	Description	Upper level of obstruction of the extrahepatic bile ducts	US/UK/Japan classification
Type 1	3%	Atresia limited to common bile duct	Common bile duct	Type 1
Type 2	6%	Cyst in the liver hilum communicating with dystrophic intrahepatic bile ducts	Hepatic duct	Type 2
Type 3	19%	Gallbladder, cystic duct and common bile duct patent	Porta hepatis	Type 2
Type 4	72%	Complete extrahepatic biliary atresia	Porta hepatis	Type 3

- Type 1 EHBA: *cholecysto-enterostomy*, or *hepatico-enterostomy*.
- Type 2 EHBA: *cysto-enterostomy*. This operation can be performed only if the hilar cyst communicates with the dystrophic intra-hepatic bile ducts (colangiography).
- Type 3 EHBA: *hepato-cholecystostomy*. The patent gallbladder, cystic duct and common bile duct are preserved. The gallbladder is mobilized with preservation of this pedicle. An anastomosis is performed between the gallbladder and the transected tissue in the porta hepatis. Since there is no direct contact between the porta hepatis and the intestine, this operation reduces the risk of postoperative cholangitis. Its specific complications are however, bile leaks and post-operative biliary ascites due to kinking and obstruction of cystic duct and common bile duct.
- Type 4: *hepatic portoenterostomy* (Kasai's procedure)



Type 4: *hepatic portoenterostomy* (Kasai's procedure)

Hepatic portojejunostomy (HPE) is the standard procedure for treatment of noncorrectable type of biliary atresia. In this procedure, the extrahepatic bile ducts are totally removed en bloc and the exposed area of the crude transected surface at the liver hilum is anastomosed to the intestine. If is present, the microscopic biliary structures drain bile into the intestine.

The common bile duct remnant is carefully dissected, because it often adheres to the surrounding tissues. After the common bile duct remnant is severed at the duodenal portion, it is pulled up and the hepatic duct is freed from underlying hepatic arteries and the portal vein, witch should be clearly identified and exposed. The hepatic ducts usually transform into a cone-shaped fibrous bile duct remnant that is located cranially to the bifurcation of the portal vein. The separation of the portal bile duct remnants from the right and left portal veins is carefully dissected posteriorly. Some surgeons recommend retraction of the main branches of the portal vein or of the branches of the portal bile duct remnants during portal dissection. The portal bile duct remnants are transected at the level of the posterior surface of the portal vein, bile sometimes comes out of the transected surface of the bile duct remnants.

After hemostasis is ensured by irrigation with warm saline, the end of the intestine is anastomosed around the transected area at the porta hepatis with full-thickness, interrupted sutures of Maxon 5-0.

A drain is placed in the foramen of Winslow, and the abdominal wound is closed in layers. (27)

There are minimum requirements to achieve *successful results of hepatic portoenterostomy*: early operation within 60 days after birth; adequate operative technique, sufficient wide proper portal dissection with full recognition to the normal anatomy of porta hepatis; precise postoperative management to increase bile flow, to prevent cholangitis, and to maintain good nutritional states; and re-do of hepatic portoenterostomy in indicated cases.

With regard to the *re-do of hepatic portoenterostomy*, favorable results were expected only in cases with active bile excretion after the initial operation. In the era of liver transplantation, the re-do portoenterostomy should be performed only in patients with sudden cessation

of good bile flow after the first operation to avoid excessive adhesion in the abdominal cavity, in patients with favorable hepatic and biliary duct remnant histology at initial operation, who do not successfully drain bile, in patients who may have had an inadequate initial surgery.

POSTOPERATIVE MANAGEMENT

-patients are placed in an oxygen tent with nasogastric drainage and given intravenous fluids.

-oral feedings is usually possible on the fifth to sixth postoperative day when bowel activity resumes.

-is used medication to avoid postoperative cholangitis:

- Choleretics

-Dehydrocholic acid, 100 mg twice daily i.v. a few months

-Ursodeoxycholic acid, 20-40 mg/kg of body weight per day, orally

-Prednisolone, 10 mg twice daily, i.v., start on the seven postoperative day for 4 days, then switch to oral administration and continue every other day.

- Antibiotics

-intravenous: Cephalosporine, 50-80 mg/kg/day for 1-2 months; Aminoglycoside, 4-8 mg/kg/day for 1-2 weeks.

-oral prophilaxis: Aminobenzyl penicillin, 200-400mg/day for 2-3 months; Cotrimoxazole, half tablet per day.

- Metabolic and nutritional care

-vitamin D supplement

-vitamin E supplement

-essential fatty acid supplement.

COMPLICATIONS

I. Cholangitis

-is the most frequent and serious complication after hepatic HPE.

-the incidences are 40% to 60% of cases.

-the cause and pathogenesis of postoperative cholangitis is not entirely clear; it is possible to be do to the reflux of intestinal contents from the draining intestinal loop toward the porta hepatis. Other explications: portal venous infections, destruction of lymph drainage at the porta hepatis, bacterial translocation.

-clinical manifestation: fever, decreased quantity and quality of bile, and a progressive increase in serum bilirubin levels; laboratory: leukocytosis, elevation of C-reactive protein levels.

-early postoperative cholangitis (within 3 months) is frequently followed by cessation of bile flow, and repeated attacks cause a progressive deterioration of hepatic function.

-in this situation, the patient should be maintained on fluid therapy and should receive heavy coverage with antibiotics and choleretics.

-6 to 9 month after surgery, the incidence of cholangitis decreases.

Modifications for prevention of cholangitis:

-Roux-en-Y biliary construction has been modified by various maneuvers: a long Roux-en-Y limb that is to50 to70 cm long, total diversion of biliary conduit, a partially diverted stoma for decompression of the biliary conduit, intestinal valve formation, and use a physiologic intestinal valve.

-many studies confirm that the Roux-en-Y with a 50-70-cm limb is the better procedure to avoid cholangitis.(28)

II. Portal hypertension

-is the most serious complication, even in jaundice free survivors.

-the incidence varies from 30% to 75%.

-cholangitis is reported to be a risk factor associated with portal hypertension.

-the presence of esophageal varices should be checked even in patients with good bile drainage.

-variceal bleeding occurs in 20-60% of patients with esophageal varices.

-the initial treatment of severe esophageal varices is endoscopic injection sclerotherapy.

-hypersplenism is another complication in long-term survivors.

-severe thrombocytopenia is found sometimes leads to alimentary tract bleeding.

III. Other complications

-hepatopulmonary syndrome: characterized by diffuse formation of intrapulmonary arteriovenous shunts, and hepatopulmonary hypertension; occasionally encountered in long-time survivors.

-intrahepatic biliary dilatation, associated with or without stones.

-malabsorbtion of fatty acids, fat-soluble vitamins and trace minerals.

-pruritus.

-retarded growth/development and delayed puberty.

-malignancies: hepatocarcinoma, hepatoblastoma, cholangiocarcinoma have been described in the cirrhotic livers of patients with EHBA in childhood or adulthood.

PROGNOSIS

- Postsurgical prognosis

-the result are different from different centers with initial success of the Kasai portoenterostomy (for achieving bile flow) ranging from 60-80%.

-one third of patients require early (<2 years) liver transplantation.

-factors that predict improved long term outcome after Kasai portoenterostomy: younger than 10 weeks at operation; preoperative histology and ductal remnant size; absence of portal hypertension, cirrhosis, and associated anomalies; experience of the surgical team; postoperative clearing of jaundice.

- Liver transplantation

-EHBA is the most common primary diagnosis in children requiring orthotopic liver transplantation.

-65% of infants undergoing the Kasai procedure ultimately required liver transplantation, including more than 50% of patients who initially achieved bile drainage.

-the primary indications for liver transplantation are the symptoms of end-stage liver disease and/or hepatic failure, including progressive cholestasis, recurrent cholangitis, poorly controlled portal hypertension,

intractable ascites, decreased hepatic synthetic function (e.g. hypoalbulinemia, coagulopathy unresponsive to vitamin K), and growth failure.

-long-term outcomes following liver transplantation in children continue to improve.

-with increased living donor availability, using split-liver grafts, application of this surgical modality for early treatment of biliary atresia (certainly, in the face of inadequate bile flow following HPE) will increase.

-some controversy exists regarding whether HPE or liver transplantation is the best initial therapy for extrahepatic biliary atresia. Transplantation certainly has been suggested as the initial procedure of choice, given its excellent long-term survival statistics and the fact that more than 60% of infants undergoing the Kasai procedure ultimately require liver transplantation. The available data indicates that overall survival statistics are not significantly altered by primary transplantation. (29)

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