Biliary Atresia and Anesthetic Considerations

42

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42.1 Introduction

Extra hepatic biliary atresia is the commonest cause of neonatal cholestasis. It is characterized by progressive inflammation, fibrosis, and eventually obliteration of extra hepatic biliary tree, leading to obstruction of bile flow. If untreated, there will be death within 2 years of life due to liver failure, portal hypertension, and cirrhosis [1].

The incidence of biliary atresia is 1 in 5000–20,000 live births with greater prevalence in Asian population and in females (F:M::1.25:1) [2, 3].

Neonates have physiologic jaundice (serum bilirubin >5 mg/dL) up to 2 weeks of life, because of increased breakdown of erythrocytes and immature hepatic enzymes. It is mainly unconjugated hyperbilirubinemia. Jaundice persisting beyond 2 weeks of life in term neonates and 3 weeks of life in preterm neonates is pathological. Conjugated hyperbilirubinemia in neonates is always pathological and is defined as conjugated bilirubin >1 mg/dL or >20% of the total bilirubin [4, 5]. Biliary atresia is one of the most common causes of conjugated hyperbilirubinemia in neonates.

42.2 Classification

1. **Ohi Classification based on anatomical involvement, into three types** (Fig. 42.1) [6]:
   (a) Type I (5%)- affects the common bile duct.
   (b) Type II a- affects the common hepatic duct. The cystic and common bile duct are patent.

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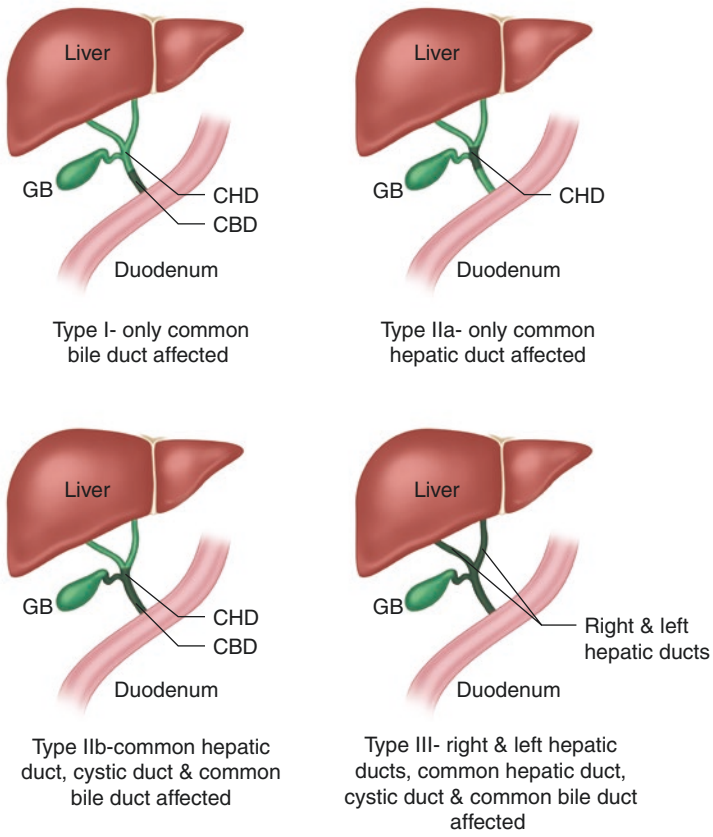

Fig. 42.1 Ohi classification of biliary atresia (CBD- Common Bile Duct, CHD- Common Hepatic Duct)

(c) Type II b- affects the common hepatic, common bile, and cystic ducts. The right and left hepatic ducts are patent.
(d) Type III (>90%)- is the commonest form and affects whole of the extra hepatic biliary system.

2. **Based on time of presentation, into two types:** [7]
   (a) **Fetal form (syndromic form)** - is present in approximately 10% neonates and manifests within first 2 weeks of life. It is associated with other congenital anomalies and syndromes like **Biliary atresia splenic malformation syndrome**, and Polysplenia syndrome **(BASM Syndrome** - Polysplenia, situs inversus, intestinal malrotation, pre-duodenal portal vein, absent infe-

rior vena cava (IVC), anomalous hepatic artery supply, cardiac defects) and is associated with poor outcome for both porto-enterostomy and hepatic transplant surgery.

(b) **Postnatal form (non-syndromic)** – is present in approximately 90% cases and manifests after 2 weeks, usually between 2–8 weeks. It is not associated with any other congenital anomalies and has a better prognosis as compared to the fetal form.

42.3 Pathogenesis

Various factors have been implicated in the pathogenesis of the disease [3, 8]:

1. **Defective embryogenesis** - extrahepatic biliary ducts are formed from ductal plate around 11–13 weeks of gestation. Ductal plate malformations may result in fetal biliary atresia.
2. **Genetic factors** involving inactivation or overexpression of certain genes.
3. **Viral infections** – most commonly associated viruses are reovirus3, rotavirus, and cytomegalovirus.
4. **Autoimmune causes** [9].

The postnatal form of biliary atresia may result from progressive inflammation of the biliary tree from exposure to virus, toxins, or autoimmune causes in the first few weeks of life [8].

42.4 Pathophysiology

42.4.1 Bilirubin Metabolism

80% of bilirubin comes from breakdown of hemoglobin and remaining from other heme containing proteins (myoglobin, cytochromes, etc.) [10]. Heme is taken up by reticuloendothelial cells and oxygenated to form biliverdin, which undergoes reduction by biliverdin reductase to form bilirubin. Bilirubin is water-insoluble and in the liver, it undergoes conjugation with glucuronic acid and becomes water-soluble which can be excreted in bile. In the gut, it undergoes hydrolysis to form stercobilinogen(urobilinogen) which then oxidizes to stercobilin. Stercobilin gives yellow color to stools. Some of the urobilinogen is reabsorbed from intestine into portal circulation (enterohepatic circulation), while some is excreted in the urine [11] (Fig. 42.2).

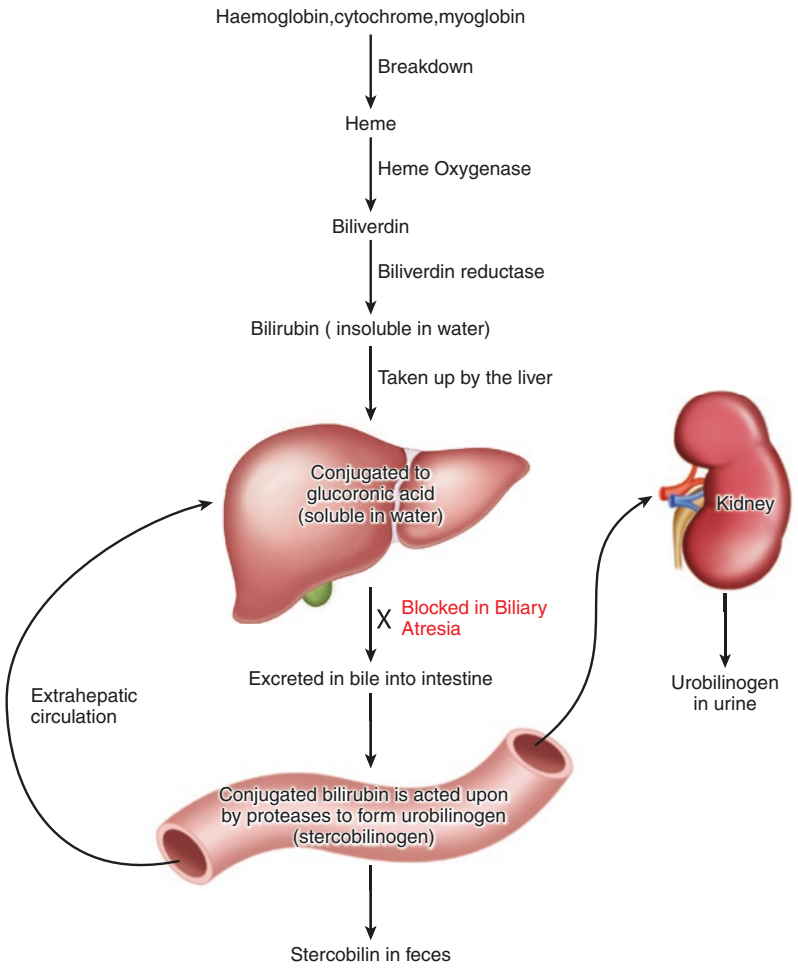

Fig. 42.2 Bilirubin metabolism and pathophysiology of biliary atresia

42.4.2 Pathophysiology

In biliary atresia, because of progressive inflammation of the biliary tract, there is obstruction to the excretion of bilirubin into bile duct, and this conjugated bilirubin starts accumulating in serum, leading to conjugated hyperbilirubinemia. No stercobilin is formed in the gut, thus acholic stools. Also, because of bile stasis there is activation of various cytokines like Tumor Necrosis Factor (TNF), Interleukin-6 (IL-6), TGF-Beta, Endothelin, Nitric Oxide(NO). These activated cytokines result in progressive fibrosis of the biliary tract and eventually cirrhosis of liver.

42.5 Signs and Symptoms

Most neonates are full term and have normal weight gain and appetite. Biliary atresia is characterized by a triad of jaundice, dark colored urine, and pale/acholic stools [1, 12].

In the fetal form, conjugated hyperbilirubinemia is present from the birth, whereas in postnatal form the physiological jaundice continues into conjugated hyperbilirubinemia. Any neonate having persistence of neonatal jaundice beyond 2 weeks of life should be worked up for biliary atresia [9].

Late presentation is associated with failure to thrive from liver failure, malabsorption of fat-soluble vitamins (vit A, D, E, K), vitamin K-dependent coagulopathy, and ascites. In late stages when the synthetic functions of liver are also affected, then coagulopathy becomes unresponsive to vitamin K supplementation [13].

42.6 Diagnosis

42.6.1 Laboratory Investigations [14]

1. **Serum bilirubin** - both total and direct bilirubin will be raised.
2. **Serum transaminases**- both ALT and AST levels are elevated.
3. **Alkaline phosphatase** - elevated levels are seen.
4. **Gamma glutamyl transpeptidase (GGT)** - is markedly increased and is used to differentiate biliary atresia from other forms of neonatal cholestasis.

42.6.2 Imaging Studies

1. **Ultrasonography**- enlarged liver and absent/contracted gall bladder is seen after 4 h of fasting [13].
2. **Doppler USG** - Hepatic artery resistance index is highly predictive of rapid deterioration in patients with biliary atresia. An index of more than 1 indicates very high mortality [15].
3. **Hepatobiliary scintigraphy (HIDA Scan)** – this use radioactive marker (Technetium Tc 99 m iminodiacetic acid). In biliary atresia uptake by the liver is normal, but there is no excretion of the isotope into the duodenum [16, 17].
4. **Percutaneous Liver biopsy** - shows fibrosis and inflammation in biliary ductules. It can help in differentiating between obstructive and hepatocellular causes of cholestasis, but it may be normal in initial stages, and serial biopsies are indicated [16].
5. **Intraoperative cholangiogram** - is the gold standard in diagnosis of biliary atresia [17].

42.7 Management

42.7.1 Medical Management Includes Supportive Treatment Like [14, 17]

- Oral antibiotics to prevent cholangitis.
- Urso-deoxy cholic acid to improve bile flow.
- Nutritional support in the form of oral fat-soluble vitamins.
- Role of corticosteroids is controversial.
- **Zinc sulfate** - in children with biliary atresia serum zinc levels are low and copper concentration is high [18]. High copper concentrations may aggravate hepatic fibrosis. Also, enzymes like DNA/RNA polymerases which help in liver regeneration contain zinc. Zinc sulphate has been used in neonatal unconjugated hyperbilirubinemia as it inhibits the enterohepatic cycle and decrease the bilirubin levels [19]. In a dose of 1 mg/kg 6 hourly, $ZnSO_4$ may have a protective effect on the liver and may also decrease bilirubin levels [20].

42.7.2 Surgery is the Definitive Treatment for Biliary Atresia

Early surgery (<6–8 weeks) has better results. **Kasai Porto Enterostomy** is done in three steps, via a large subcostal incision - [21]

1. Dissection at porta hepatis and removal of all atretic bile ducts. During this step, during exteriorization of liver and surgical retraction, there might be kinking of IVC, leading to decrease in venous return and severe hypotension,
2. Preparation of Roux-en-Y loop of jejunum, and.
3. Anastomosis of functional bile ducts to the jejunal loops which will allow bile drainage.

Prognosis depends on: [22]

1. Age at which surgery is done (< 8 weeks better prognosis),
2. Preoperative histology and remnant duct size,
3. Absence of portal hypertension,
4. Absence of congenital syndromes like BASM,
5. Post-op rapid clearing of bilirubin levels, and
6. Experience of surgical team.

Unfortunately, only 50–60% of Kasai Porto enterostomy are successful and most babies eventually need liver transplantation. Biliary atresia is in fact the most common indication for orthotopic liver transplant [6].

42.8 Anesthetic Management

A neonate with biliary atresia may require anesthesia for various procedures:

- Liver biopsy
- Intraoperative cholangiogram
- Upper GI endoscopy
- Kasai Porto enterostomy
- Revision surgeries

Anesthesia for these children is challenging not only because of their age, but also because of their pathology.

- **Airway**- these children should always be considered as full stomach because of abdominal distension due to ascites or hepatosplenomegaly. So, even for small procedures like endoscopy, airway should be secured with an endotracheal tube. Also, enlarged liver may cause splinting of diaphragm and decrease FRC, which makes them more prone to desaturation during periods of apnea as compared to normal infants [23].
- **Coagulopathy**- in early stages, coagulopathy is vitamin K-responsive as it is because of malabsorption of fat-soluble vitamins (vitamin K). In the later stages, when synthetic function of the liver also gets affected, then coagulopathy is because of decreased synthesis of clotting factors by the liver and is no longer responsive to vitamin K [24].
- **Drug metabolism**- hepatic metabolic function is affected in the late stages of the disease, so drug dosages may have to be altered [23].
- **Good postoperative pain relief** is required for early extubation. Doses of opioids and local anesthetics may have to be altered and post-op monitoring in NICU is essential.

42.9 Anesthetic Management of a Child Coming for Kasai Porto Enterostomy

42.9.1 Preoperative Preparation

1. **Medical management** is continued which includes:
   a. Injection vitamin K (1–2 mg/kg/day) IM for 3 days prior to surgery
   b. CBC, coagulation profile and LFT should be done
   c. Arrange for blood and FFP (10–15 ml/kg)
   d. NPO 4 hours for breast milk and 6 hours for formula feed

   Note - Written informed consent should be taken from the parents or guardians informing about the high risk of procedure, need for central venous access, need for postoperative ICU stay, and possible need for postoperative ventilation.

42.9.2 Intraoperative Management

Usually, the baby will have an IV canula in situ. In case not, then an inhalational induction can be done with sevoflurane in oxygen and nitrous oxide and then an IV can be placed. Obtaining a good IV line may be difficult in these neonates because of prolong hospital stay and multiple attempts at IV access. Venous access should preferably be achieved in upper limb veins which drain into SVC as IVC may get kinked or occluded intraoperatively when liver is exteriorized.

IV induction can be done using propofol since propofol metabolism is not much altered in liver disease as it is mainly metabolized via extra hepatic route [25, 26]. Barbiturates (Thiopentone), on the other hand, have a major hepatic metabolism and dose adjustment may be required [27]. Once induced, muscle relaxation can be achieved with atracurium or cisatracurium [28]. Cisatracurium has an advantage of less formation of laudanosine (a neurotoxic metabolite excreted by the liver). Trachea should be intubated with appropriate size endotracheal tube and a gastric tube (8–10 Fr) inserted.

A central line should be placed if coagulation profile is normal. In case of coagulopathy, a PICC line can be placed. Arterial cannulation is indicated in selected cases with cardiac anomalies.

Intraoperative monitoring includes ECG, pulse oximetry, NIBP, temperature, $EtCO_2$, and blood sugar. Central line may be used to measure CVP.

For maintenance of anesthesia, O_2 air mixture should be used. Nitrous oxide may cause distension of the gut and is better avoided [29]. Halothane should be avoided because of its potential hepatoxicity [27]. Desflurane, isoflurane, and sevoflurane can all be used for maintenance as all preserve hepatic blood flow and produce very little hepatotoxic metabolites [30]. Desflurane preserves hepatic flow better than sevoflurane. Also, it is metabolized to a lesser extent (0.02%) as compared to sevoflurane (5%). So, desflurane may be a better choice in these patients [31].

Opioids should be used intraoperatively for pain relief, preferably the short acting opioids like fentanyl or remifentanil. Morphine in a dose of 0.05–0.1 mg/kg has also been used [32].

42.9.3 Intraoperative Anesthetic Goals

Main intraoperative goals are to maintain euvolemia, euthermia, euglycemia, and hepatic blood flow.

i. **Euvolemia -** maintenance fluids are administered in the form of crystalloids, given at a rate of 10 mL/kg/h. 2% dextrose should be added in the first fluid as these babies are prone to hypoglycemia [33]. Blood sugars can be checked after 1–2 h, and dextrose added if sugars are low. Since it is a major open surgery, large volume fluid and blood losses are expected. Losses should be replaced with crystalloids. Blood loss exceeding 10% of total blood volume should be replaced by warm and fresh blood preferably not more than 5 days old [29].

ii. **Euthermia** should be always ensured by using warming blankets, in fluid warmers, warm irrigation fluids, warm blood, and blood products and covering the baby with cotton or plastic sheets.

iii. **Euglycemia** - Blood sugars are checked every 1–2 hours and dextrose added if sugar levels are low to maintain euglycemia.

$EtCO_2$ (End tidal carbon dioxide) should be maintained in normal range to prevent changes in hepatic and portal blood flow.

iv. **Hepatic Blood Flow** - Sudden drop in blood pressure is seen when liver is exteriorized. This is because of kinking of IVC (inferior vene cava) and consequent decrease in venous return to the heart. This is seen as decrease in amplitude of R wave on ECG [34], phenomenon known as **Brody's effect**. Fluid boluses of 10–20 mL/kg can be given to prevent hypotension [24], but avoid excessive fluids as this may lead to distension of liver capsule causing its rupture and hemorrhage. If hypotension is not corrected by 20 mL/kg fluid, then vasopressors should be started.

Sometimes, bradycardia may occur as a vagal response to liver traction. Releasing the traction usually is corrective in these cases. If it persists, atropine can be given.

v. **Extubation** - The neonate can be extubated at the end of surgery if respiratory efforts are adequate and no contraindication for extubation is present. The baby should be kept in NICU after surgery.

42.9.4 Postoperative Analgesia

Kasai Porto enterostomy is a major abdominal surgery and multimodal pain management is required for good recovery.

42.9.4.1 Epidural Block (Fig. 42.3)

Epidural block lowers the need for intra and postoperative opioids and also the need of postoperative ventilation [35]. An epidural catheter can be inserted from caudal, lumbar, or thoracic space. The tip of the catheter should be at T7–T8 thoracic level. It is important that care is taken while performing lumbar or thoracic epidural so as not to injure the spinal cord. The contraindications to epidural placement should be ruled out in every case (parental/ surgeon refusal, coagulopathy, spinal, or vertebral anomalies or any local or systemic infection) [36, 37].

Caudal block can also be given upto a volume of 1–1.5 mL/kg, using either bupivacaine or ropivacaine and additives (morphine) for extended pain relief but it is unlikely to cover all the required dermatomes [38].

42.9.4.2 Peripheral Nerve Blocks

Peripheral nerve blocks such as rectus sheath block, erector spinae block, and quadratus lumborum block can also be given, but under ultrasound guidance [39]. These are simple to perform and safer as there are no major vessels involved.

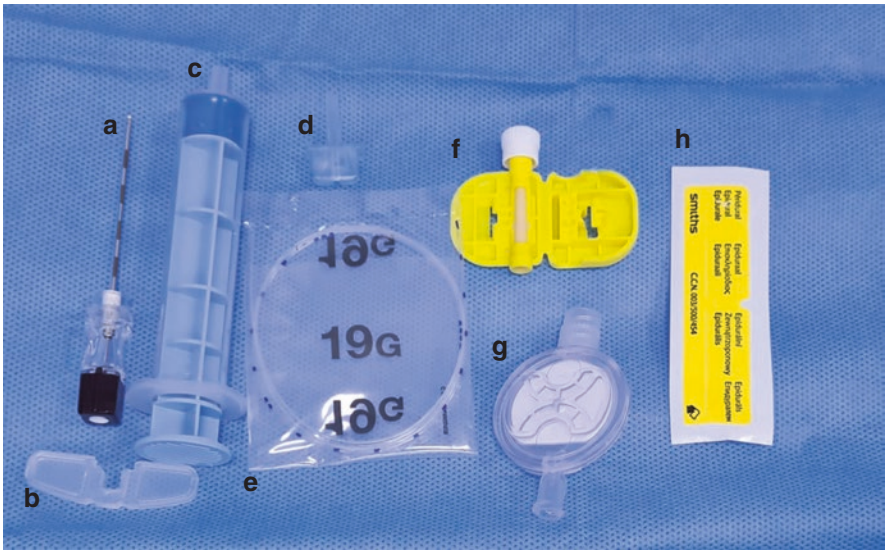

Fig. 42.3 Pediatric Epidural set (**a**) 19G Tuohy needle, 5 cm in length with transparent hub; (**b**) removable wings; (**c**) 10 mL loss of resistance syringe; (**d**) introducer; (**e**) 19G catheter; (**f**) luer-lock connector for the catheter; (**g**) bacterial filter; (**h**) label (yellow in color)

Continuous infusions can also be given, though the data are limited. Thoracic paravertebral block has also been used by some in these neonates [40].

Local anesthetics like bupivacaine or ropivacaine can be used with or without opioids. There are higher chances of cardiac toxicity with bupivacaine because of decreased hepatic clearance and increase in unbound fraction. But it has been seen that postsurgery there is an increase in level of alpha1 acid glycoprotein (AAG) and bupivacaine metabolism is similar in both infants with and without biliary atresia [41]. Recommended maximum dose of bupivacaine is 0.25 mg/kg/h in <4-month-old. Ropivacaine is less cardiotoxic and is a better option for epidural infusions in neonates. Recommended dose is 0.9–2 mL/kg bolus of 0.2% ropivacaine followed by infusion (0.2 mL/kg/h). The epidural infusions can be safely used for 48–72 h [42]. Postoperative removal of epidural catheter should be done only after getting a coagulation profile.

42.9.4.3 Intravenous Paracetamol

Intravenous paracetamol in a dose of 20 mg/kg bolus followed by 10 mg/kg 6 hourly is safe and provides a good pain relief [43, 44].

42.9.4.4 Systemic Opioids

Systemic opioids - synthetic and metabolic functions of liver are unimpaired at early stages. Also, because of the hepatic artery buffer response (HABR), the total hepatic blood flow is not altered in babies with biliary atresia. Thus, opioids usually

do not require dose modifications [32]. But postoperative monitoring to watch out for any respiratory depression is a must in patients receiving opioid infusion [45]. Naloxone should be readily available. Morphine can be used with a loading dose of 0.05 mg/kg followed by infusion with 10–40 mcg/kg/h up to a maximum of 1 mg/kg/day. Fentanyl can be used with a loading dose of 1mcg/kg followed by 1 mcg/kg/h. Tramadol has been also used in a dose of 1 mg/kg 12 hourly [24, 46]. Local infiltration at incision site also provides some pain relief.

42.10 Conclusion

Any neonate presenting with conjugated hyperbilirubinemia should be suspected of having biliary atresia. Most neonates are healthy, have good appetite and weight gain at presentation. Only presenting symptom of the disease may be jaundice persisting beyond 2 weeks of life. Early surgery has a better prognosis. Kasai Porto Enterostomy is challenging for the anesthetist. All precautions pertaining to normal surgical neonate must be kept in mind. In addition, these neonates may pose airway related challenges, may have coagulation abnormalities and altered drug metabolism. Good intraoperative and postoperative analgesia is also fundamental for expediting the recovery of the neonate after surgery. However, this procedure should be carried out in a center that has NICU and has provision for ventilation of these babies.

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