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Review Article

Neonatal cholestasis revisited!

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ABSTRACT

Cholestasis in infantile age group occurs approximately in 1 in 2500 term babies and is often missed out by primary care physicians in the setting of physiologic jaundice. It suggests hepatobiliary dysfunction and is always pathologic. Any infant noticed to be jaundiced after 2 weeks should be evaluated for conjugated hyperbilirubinemia and an elevated direct bilirubin of more than 1 mg/dl merits timely evaluation and management. The most common causes of neonatal cholestasis are biliary atresia (25–40%) followed by monogenetic disorders (25%) and many other unknown or multifactorial causes. Once cholestasis is diagnosed, a systematic approach is the key to reach the diagnosis and to initiate specific treatment, which in many cases is lifesaving. In this review article, we aim to provide a better work approach, clinical overview of potential differential diagnosis, and treatment recommendations for timely diagnosis and management of neonatal cholestasis.

1. Introduction

Jaundice is a common complaint that can occur in 2.4–15% of newborns during the first two weeks of life.[1] It is mostly due to rise in unconjugated bilirubin, and resolution occurs spontaneously in most cases. Prolonged jaundice is defined as jaundice lasting for more than 14 days or recurring after the second week of life.[2,3] Unconjugated hyperbilirubinemia is usually benign, and it requires careful evaluation to differentiate it from conjugated hyperbilirubinemia which is always pathological and indicates hepatobiliary dysfunction. Clinical features and laboratory findings of many disorders leading to cholestasis are similar. Many of these pathologies have specific medical or surgical treatment. Even when specific treatment is not available, these children may benefit from early supportive treatment. Therefore, it is important to timely diagnose neonatal cholestasis so as to prevent the complications.[4] This article provides an overview of the approach to an infant with cholestasis, diagnostic evaluation, differential diagnosis, and management recommendations.

2. Definition and incidence

Cholestasis is defined physiologically as a significant reduction in bile flow, pathologically as the presence of bile pigment in hepatocytes and bile ducts on histology, and clinically as accumulation of bile contents (bilirubin, bile acids, and cholesterol) in blood and extrahepatic tissues. It occurs as a result of impaired bile formation by hepatocytes or due to obstruction to the flow of bile through the intrahepatic or extrahepatic biliary tree. The overall incidence of neonatal cholestasis is around 1 in 2500 live births.[5,6] Neonatal cholestasis was conventionally defined as conjugated bilirubin more than 1 mg/dl, if the total serum bilirubin is $\leq$ 5 mg/dl, or >20% of total serum bilirubin when it is > 5 mg/dl.[7,8] Recently, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidelines on neonatal cholestasis recommended to consider it to be abnormal if the direct bilirubin level was more than 1 mg/dl regardless of the total bilirubin[9].

3. Clinical presentation

The clinical presentation of neonatal cholestasis varies in relation to its etiology. The most common findings are prolonged jaundice, dark yellow urine, acholic stools, and hepatomegaly. The presence of pigmented stools indicates patency of biliary system and makes extrahepatic biliary atresia (EHBA) unlikely. On the other hand, acholic stools are suggestive but not diagnostic of extrahepatic biliary obstruction as it can also be present in severe intrahepatic cholestasis. Many times, the parents are not able to identify acholic stools, and in the early course of EHBA, stools may appear normal or intermittently pigmented; so, it is important for the physician to assess the stool color himself serially. Children with EHBA are usually thriving well and generally not sick. In sick infants (poor feeding, lethargy, shock, coagulopathy, ascites, or

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hypoglycemia), sepsis or metabolic disorders such as galactosemia, tyrosinemia, mitochondrial hepatopathies, gestational alloimmune liver disease (GALD), primary hemophagocytic lymphohistiocytosis (HLH), or herpes simplex virus (HSV) infection should be suspected. These should be investigated promptly to find the etiology as many of these disorders are amenable to specific therapies and have good prognosis provided the treatment is started early in the phase of illness. Splenomegaly is present in infants with infections, cirrhosis, portal hypertension, and storage or hemolytic disorders. The spleen is usually of normal size early in the course of illness in EHBA, but the size of the spleen increases with advancing age.

4. Evaluation of the jaundiced infant

Jaundice at 2 weeks of age should alert the physician to rule out cholestasis. Any formula–fed infant with jaundice after 2 weeks of age should be evaluated for cholestasis. Breastfed babies who appear otherwise well and have no history of dark urine or acholic stools may be followed up clinically until 3 weeks of age, and if they are still icteric, then serum total and conjugated bilirubin should be estimated.[10]

5. History

A detailed prenatal and neonatal history should be noted. History of prematurity, low birth weight, neonatal sepsis, parenteral nutrition, and hospitalization should be elicited. Details about onset of jaundice, changes in stool pigmentation, and urine color should also be noted carefully. History of poor feeding, lethargy, vomiting, seizures, and poor weight gain may indicate sepsis or some metabolic disorder. Positive family history for similar complaints or consanguinity points toward genetic disorders, whereas bad obstetric history may indicate maternal infections (Toxoplasma, Rubella, CMV and Herpes [TORCH]) or GALD. History of cholestasis and pruritis in mother during the last trimester of pregnancy points toward progressive intrahepatic cholestasis of pregnancy (IHCP), and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome occurs in mothers of babies with fatty acid oxidation defects (FOADS).[11] Bleeding, especially hematoma formation, at injection sites or mucosal bleeds may occur as a result of coagulopathy due to vitamin K deficiency or deranged synthetic function of liver. The potential clues to identify the underlying disorder are listed in Table 1.

Table 1
Potential clues to specific etiologies.

A.	Dysmorphism
	Alagille syndrome
	Trisomies
	Micropenis: hypopituitarism
	Chubby cheeks: citrin deficiency
	Cleft palate: kabuki syndrome
B.	Neurologic abnormalities
	Niemann–Pick type C
	Congenital disorders of glycosylation
	Septo-optic dysplasia (hypopituitarism)
C.	Early-onset severe liver dysfunction
	Herpes simplex virus infection
	Neonatal iron storage disease
	Tyrosinemia type 1
	Galactosemia
	Niemann–Pick type C
	Hemophagocytic lymphohistiocytosis
	Mitochondrial respiratory chain defects
	Bile acid synthetic disorders
D.	Renal disease
	Tyrosinemia type 1
	Alagille syndrome
	Arthrogryposis-renal tubular dysfunction-cholestasis syndrome (ARC)
E.	Cholestasis/pruritis but anicteric
	PFIC type 2
	Bile acid synthetic disorders
	Familial hypercholanemia
F.	Family history
	Alagille syndrome (autosomal dominant)
	PFIC 1 and 2 (autosomal recessive)
	Galactosemia and tyrosinemia (autosomal recessive)
	Neonatal iron storage disease
	Cystic fibrosis (autosomal recessive)
G.	Maternal history of hepatobiliary problems
	Intrahepatic cholestasis of pregnancy: PFIC 2
	Preeclampsia with HELLP: Fatty acid oxidation disorders
H.	Low or normal serum GGT
	PFIC 1 or 2
	Bile acid synthetic disorders
	Tight junction protein (TJP) type 2 defect
	Endocrine causes
	Arthrogryposis-renal tubular dysfunction-cholestasis syndrome
	Lymphedema cholestasis syndrome (Aagenaes syndrome)

HELLP, hemolysis, elevated liver enzymes, and low platelets; PFIC, progressive familial intrahepatic cholestasis.

6. Physical examination

A thorough physical examination plays a very important role in the evaluation of a jaundiced infant. It should not only focus on the abdomen but also take into account the extrahepatic features such as dysmorphism, growth and development, and cardiac, pulmonary and neurological examination as well (Table 2).

7. Investigations

In addition to laboratory investigations, imaging and liver histopathology are important in evaluating infants with neonatal cholestasis. The first objective is to identify the diseases amenable to specific therapies and to differentiate between medical and surgical causes. Bacterial sepsis, HSV, hypopituitarism, and metabolic disorders such as galactosemia and tyrosinemia can cause rapid deterioration and should be excluded early in the diagnostic process.

7.1. Biochemical investigations

Numerous biochemical parameters have been used in an effort to distinguish between infants with intrahepatic versus extrahepatic obstructive cholestasis. Standard liver tests show nonspecific and variable elevation of bilirubin, aminotransferases, alkaline phosphatases, and lipids. Serum glucose, albumin, and coagulation profile reflects the synthetic function of the liver. Persistent coagulopathy out of proportion to degree of cholestasis is an early indicator of metabolic liver disease such as tyrosinemia type 1 or GALD. Nonglucose-reducing substance may be tested bedside to rule out galactosemia (false negative in children who are fasting, are on lactose-free formula, or have received blood transfusion recently). Increased urinary succinylacetone is pathognomic of tyrosinemia. Elevated ferritin levels more than 1000 ng/ml are seen in patients with GALD.[12] Serum alpha fetoprotein levels are high at birth and then subsequently reduce in the postnatal period.[17] Excessively high levels are characteristically seen in children with tyrosinemia and citrin deficiency (also associated with raised ammonia levels), as well as in few infants with idiopathic neonatal hepatitis.[18] Low serum cholesterol with dysmorphism and neurologic abnormalities suggest peroxisomal disorder. Table 3 outlines a staged approach that excludes early treatable life-threatening conditions first and then considers investigations relevant for more common conditions and finally those targeted at rarer disorders.

Table 2
Physical examination in children with neonatal cholestasis.

General health: Sick appearance may point toward sepsis or metabolic disorders as listed in Table 1. Children with extrahepatic biliary atresia are usually well thriving and appear well. Small for gestational age at birth or failure to thrive later occurs with congenital infections or chromosomal disorders.[12]
Stool examination: The physician should examine the stool for pigment himself serially on multiple occasions. Acholic stools are suggestive of extrahepatic biliary atresia or biliary obstruction.
Dysmorphism: Facial dysmorphism is seen in Alagille syndrome (broad nasal bridge, triangular facies, and deep-set eyes).These typical features appear around six months of age. Dysmorphism may also be seen in trisomies (13, 18, and 21). Infants with citrin deficiency characteristically have 'chubby cheeks'[13]
Skin: Complications of cholestasis such as bruising, xanthomatosis, or scratch marks. Ichthyosis may suggest neonatal sclerosing cholangitis (NISCH), and contractures may suggest arthrogryposis-renal tubular dysfunction-cholestasis syndrome (ARC)[14,15]
Ocular abnormalities are seen in Alagille syndrome (posterior embryotoxon), galactosemia (cataract), storage disorders (cherry red spot), congenital infections (chorioretinitis), and in septo-optic dysplasia.
Hearing abnormalities may be present in PFIC 1, tight junction protein (TJP) defects, and mitochondrial disorders
Cardiac: Murmurs and features of congestive cardiac failure may point toward underlying congenital heart disease which may be present in Alagille syndrome (peripheral pulmonary stenosis and Tetralogy of fallot) and in biliary atresia splenic malformation syndrome.[16]
Abdomen: Firm hepatomegaly often with a prominent middle or left lobe is seen in EHBA. Splenomegaly in EHBA appears after the newborn period, and if present at a young age of 2–4 weeks, it should point toward other diseases such as storage or hematologic disorders. Ascites may be present in advanced liver disease due to biliary atresia or due to liver failure in metabolic disorders.
Miscellaneous: Butterfly vertebrae in Alagille syndrome and micropenis in hypopituitarism

EHBA, extrahepatic biliary atresia; PFIC, progressive familial intrahepatic cholestasis.

Table 3
Investigations in neonatal cholestasis.

Initiate investigations to detect readily treatable disorders and to assess the severity of liver involvement
Liver function test (TSB/DSB, SGOT, SGPT, ALP, GGT, albumin, and prothrombin time)
Complete blood count
Bacterial cultures of blood/urine
Thyroid profile
Fasting ultrasound
Targeted evaluation for conditions requiring prompt specific therapy as indicated
Urine reducing substances and GALT assay
Serum bile acids
Serum iron ferritin
Viral PCR: CMV, HSV, HHV-6, and enterovirus
Urine succinylacetone
Alpha-1-antitrypsin level and phenotype
Liver biopsy
Per-operative cholangiogram
Serum ammonia
Urine and plasma amino acids
Serum cholesterol
Ophthalmologic examination: posterior embryotoxon, retinopathy, and cataract
Cardiac evaluation by 2D ECHO: peripheral pulmonary stenosis in Alagille syndrome
Urine fast atom bombardment mass spectroscopy for abnormal bile acid metabolites
Other specific tests if indicated
Karyotype
Very-long-chain fatty acids
Plasma acylcarnitines
Bone marrow examination
Genetic testing: Cystic fibrosis, Alagille syndrome, PFIC disorders

ALP, alkaline phosphatase; CMV, Cytomegalovirus; DSB, direct serum bilirubin; GALT, galactose-1-phosphate uridyl transferase; GGT, gamma-glutamyl transferase; HHV, Human herpes virus; HSV, herpes simplex virus; PCR, polymerase chain reaction; PFIC, progressive familial intrahepatic cholestasis; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; TSB, total serum bilirubin.

7.2. Role of gamma-glutamyl transferase (GGT) in neonatal cholestasis

Gamma-glutamyl transferase (GGT) value is high in neonates than in older children and is generally elevated in cholestasis. In some cholestatic disorders, including progressive familial intrahepatic cholestasis type 1 (PFIC 1), PFIC 2, bile acid synthetic defect, ARC syndrome, endocrine defects, and tight junction protein (TJP) type 2 deficiency, GGT is normal or low at presentation (as listed in Table 1).[19–24] Apart from these, initial low/normal GGT may also be seen in patients with neonatal hepatitis, citrin deficiency, or mitochondrial disorders.[22,25] Conditions such as syndromic (Alagille syndrome [AGS]) and nonsyndromic bile duct paucity and, often but not always, biliary atresia present with high GGT.[26] Patients with initial GGT value of less than 75 U/L or more than 300 U/L were found to have poor prognosis compared with patients with GGT value between 75 and 300 U/L.[22] For patients with GGT levels less than 75 U/L, serum bile acids should be measured. In patients with elevated serum bile acids, genetic analysis of ATP8B1 (FIC1 for PFIC 1) or ABCB11 (BSEP for PFIC2) should be undertaken. Low serum bile acids merit workup for rare disorders of bile acid synthesis.[27]

8. Diagnostic imaging

A fasting ultrasound is the imaging of choice to assess the obstructive lesions of biliary tree such as choledochal cyst and to look for signs of advanced liver disease and vascular or splenic abnormalities.[28] Several ultrasound features such as abnormal gall bladder morphology, lack of gall bladder contraction after feeding, nonvisualization of common bile duct, triangular cord sign, hepatic artery diameter, and the ratio of hepatic artery to portal vein diameter aid in the diagnosis of EHBA.[29–32] A structure less than 15 mm in length located in the expected region with irregular margins and without a well-defined wall excludes a normal gall bladder.[33] Triangular cord sign is a cone-shaped echogenic fibrous structure at the porta measuring more than 3 mm in thickness, and it is associated with high sensitivity (73–100%) and specificity (98–100%) for biliary atresia.[34,35]

Hepatobiliary scintigraphy or hepatobiliary iminodiacetic acid scan (HIDA) scan is used to confirm biliary tract patency. It has high sensitivity for biliary atresia (83–100%) but lacks specificity (68.5–72.2%).[36–38] An excretory scan virtually rules out EHBA because false-negative results are extremely rare. The test is non-diagnostic when there is no tracer excretion because patients with bile duct paucity, idiopathic neonatal hepatitis, and low birth weight and those receiving parenteral nutrition (PN) may also have nonexcretory HIDA scans.[39] Phenobarbitone is usually administered for 5 days before performing the scan in an attempt to enhance biliary excretion of the isotope and increase its discriminatory value. This leads to unnecessary delay in the diagnosis of EHBA.[40]

Endoscopic retrograde cholangio-pancreatography (ERCP) has been proved effective and has high positive predictive value (PPV) and negative predictive value (NPV) (sensitivity: 86–100%, specificity: 87–94%, PPV: 96% and NPV: 100%).[41,42] However, it requires advanced equipment and an experienced endoscopist, which are not available readily at many centers. The diagnostic value of magnetic rasonance cholangio-pancreatography (MRCP) for biliary atresia was evaluated recently, and specificity of 36% and sensitivity of 99% were reported.[43]

9. Histopathology

Ultrasonography (USG)-guided liver biopsy is considered safe in children with an estimated complication rate of 1.7%.[44] It helps in differentiating between obstructive and intrahepatic causes in 90–95% of cases.[45] The classic histologic features of biliary atresia

are portal tract expansion, bile ductular proliferation, and bile plugs with preserved hepatic lobular architecture. The liver biopsy findings may be nonspecific if biopsy is performed very early in the course of disease.[46,47] Other disorders that may mimic biliary atresia on liver biopsy are cystic fibrosis, alpha-1 antitrypsin deficiency, or PN-induced hepatitis. In idiopathic neonatal hepatitis, there is lobular disarray, inflammatory cells in the portal tract, and giant cell transformation on liver biopsy.[48] Giant cell transformation may also be seen in 20–50% of patients with biliary atresia. In PFIC 1, small, tidily arrayed hepatocytes and pallid intracanalicular bile are seen, and in PFIC 2, bile is khaki colored rather than greyish. Bile pigment accumulates in hepatocytes and canaliculi, with hepatocellular giant cell change and necrosis. Portal tract changes or bile plugs are not seen in both. Other significant features identified on liver biopsy are bile duct paucity, cytomegalo virus (CMV) inclusion bodies, steatosis, etc. The extent of fibrosis on liver biopsy also helps in prognosticating the outcome after Kasai portoenterostomy.[48]

10. Intraoperative cholangiogram

Intraoperative cholangiogram and histological examination of duct remnants are the gold standard for the diagnosis of extrahepatic biliary atresia.[49] Intraoperative cholangiogram is carried out if liver histopathology and clinical features are suggestive of biliary atresia. It may be false positive (nonvisualization of the extrahepatic biliary tree) in up to 20% of cases, especially in patients with AGS, cystic fibrosis, or hypoplastic biliary tree.[50]

11. Management of neonatal cholestasis

The primary objective in the management of neonatal cholestasis is to identify the diseases amenable to specific treatment such as sepsis, urinary tract infection, hypothyroidism, galactosemia, tyrosinemia, HSV, HLH, GALD, CMV, biliary atresia, and choledochal cyst. In the remaining diseases, when there is no specific treatment, the treatment is aimed at treating the complications of long-standing cholestasis such as malnutrition, deficiency of fat-soluble vitamins, pruritis, hypercholesterolemia, cirrhosis, portal hypertension, and liver failure.

11.1. Nutritional management

Calorie intake should be 125% of the recommended dietary allowance based on ideal body weight.[3] In cholestasis, medium chain triglycerides (MCT) are more readily absorbed than long chain triglycerides (LCT) as they are water soluble, do not require micelle formation by bile acids, and are directly absorbed into the portal circulation. Similarly, bile acids are also required for the intestinal absorption of fat-soluble vitamins resulting in the deficiencies. Doses of at least two to four times the recommended daily allowances (Table 4) are to be given, and vitamin supplementation should continue for at least 3 months after the resolution of jaundice (Table 5).

11.2. Management of pruritis

Ursodeoxycholic acid (UDCA) is a choleretic agent and is used as first-line therapy for pruritis due to cholestasis. Its mode of action is not exactly understood, but two main mechanisms are substitution of hepatotoxic with nontoxic hydrophilic bile acids in the bile acid pool and stimulation of bile flow. The recommended dose is 20–30 mg/kg/dose in two to three divided doses.[51] The only side effect is diarrhea, which usually responds to dose reduction. Rifampicin is indicated in the treatment of pruritis as it induces hepatic microsomal enzymes and inhibits bile acid uptake by hepatocytes.

Table 4
Medical management of neonatal cholestasis.

Malabsorption/Malnutrition:	**Fat-soluble vitamin supplementation:**
Optimize calorie intake	Vitamin A: 5000–25000 U/day
MCT: 30–50% of total fat as MCT	Vitamin D: 400–1200 IU/day
Enteral tube feeding/parenteral nutrition	Vitamin E: 15–25 IU/Kg/day
	Vitamin K: 2.5 twice a week to 5 mg once a day
	Water-soluble vitamin: 1–2 times of RDA
	Ca/P/Mg/Zn/Fe supplementation
Pruritis:	**Ascites:**
Ursodeoxycholic acid	Sodium restriction
Cholestyramine	Diuretic therapy:
Rifampicin	Spironolactone and furosemide
Naloxone	Antibacterial prophylaxis
Partial external biliary diversion	Albumin transfusion
	Therapeutic paracentesis
Portal hypertension and variceal hemorrhage	**End-stage liver disease/refractory symptoms**
Endoscopic variceal ligation/sclerotherapy	Liver transplantation
Surgical shunt procedure	
Liver transplantation	

MCT, medium chain triglycerides; RDA, recommended dietary allowance.

Table 5
Specific management of cholestatic disorders.

Extrahepatic biliary atresia	Kasai portoenterostomy
Hypothyroidism	Thyroxine replacement
Hypopituitarism	Hormone replacement therapy
Galactosemia	Galactose-free diet
Tyrosinemia	NTBC and low-tyrosine diet
Congenital CMV	Ganciclovir
Herpes simplex infection	Acyclovir
Neonatal hemochromatosis	IVIg, Plasmapheresis, and antioxidant cocktail
Intestinal failure–associated liver disease	Encourage enteral diet and treatment of sepsis

CMV, cytomegalovirus; NTBC, nitro-trifluoromethylbenzoyl-cyclohexanedione.

Liver function should be monitored for potential hepatotoxicity, and the recommended dose is 10 mg/kg/day. Cholestyramine is useful in resistant pruritis and severe hypercholesterolemia in cholestasis. It binds with intestinal bile acids and cholesterol and prevents their reabsorption. The recommended dose is 250 mg/kg/day, and the known side effects are metabolic acidosis, steatorrhea, and constipation.[7] Phenobarbital enhances bile acid synthesis, stimulates bile acid flow, induces microsomal enzymes, and thus lowers circulating bile acid pool. The recommended dose is 3–10 mg/kg/day, but sedation and behavioral side effects limit its use.

12. Specific diseases

12.1. Extrahepatic biliary atresia

EHBA is an idiopathic fibrosing cholangiopathy that leads to obstruction of the extrahepatic bile duct leading to biliary cirrhosis. It accounts for approximately one-third of the cases of neonatal cholestasis.[52] Most of the children with EHBA are born from a normal pregnancy, show normal postnatal growth, generally have prolonged jaundice, and develop acholic stools at 3–6 weeks of age.[8] There are two forms: 80% have isolated biliary atresia (perinatal) without any other congenital malformations, have normal early growth, and develop or have persistent jaundice and the remaining 20% of infants have embryonic form of biliary atresia, these have congenital malformations (biliary atresia splenic malformation syndrome, splenic and hepatic vascular anomalies, situs

inversus, congenital heart disease etc.).[53] These infants are jaundiced at birth and remain so. Biochemical findings, abdominal ultrasound, and hepatobiliary scintigraphy can be suggestive but are not diagnostic. Liver biopsy is diagnostic but can be ambiguous in 10% of the patients, especially if performed before 6 weeks of age.[10] The standard management is intraoperative cholangiogram followed by Kasai portoenterostomy if the cholangiogram is obstructive. The success rate depends on the age of the child at the time of portoenterostomy and the expertise of the surgeon. The success rate is up to 80% if the surgery is done at less than 30–45 days of age and is less than 20% if performed after 90 days of age.[54] The extent of fibrosis in the liver histopathology can prognosticate the success after portoenterostomy, and in children with extensive fibrosis, where there are high chances of failure, primary liver transplant (LT) can be planned.

Although Kasai hepatoportoenterostomy improves survival with native liver, more than 70% of patients with biliary atresia will ultimately require LT.[55] Indications for listing for liver transplantation include progressive cholestasis, recurrent episodes of cholangitis, deterioration of hepatic synthetic function, and severe portal hypertension. Current survival for liver transplantation in children has achieved excellent short-term outcomes with 1-year patient and graft survival in more than 95% for elective cases.[56] After transplant, lifelong immunosuppressive therapy is required, leading to increased risk of opportunistic and community-acquired infections necessitating a close medical and surgical supervision. Long-term complications include side effects of immunosuppression, CMV or EBV infection, posttransplant lymphoproliferative disease (PTLD), late biliary stricture, late hepatic artery or portal vein thrombosis, and acute or chronic rejection. Most of the survivors have a good quality of life, attend school, and have normal growth.

12.2. Idiopathic neonatal hepatitis

It accounts for 25–30% of the patients with neonatal cholestasis.[2,3] It is not a specific pathology but represents an exclusion diagnosis with liver histopathology showing lobular disarray, focal hepatic necrosis, and giant cell transformation. The portal tracts are relatively normal. These infants are more frequently preterm and may have intrauterine growth restriction (IUGR). Cholestasis occurs after a few weeks of birth and is associated with hepatomegaly, mild to moderate transaminitis, and normal or low GGT. Acholic stools are uncommon and, if present, indicate adverse prognosis. Management is mostly supportive with nutritional supplementation and treatment of complications. Prognosis is fair with 90% patients recovering by the age of 1 year. There is however 1% recurrence rate in subsequent siblings.[2]

12.3. Progressive familial intrahepatic cholestasis

Progressive familial intrahepatic cholestasis (PFIC) is a group of unrelated monogenic disorders characterized by mutations in one of the genes involved in canalicular bile acid transport system, leading to impaired bile formation, progressive intrahepatic cholestasis, and liver injury. PFIC 1 is caused by mutation in the ATP8B1 gene (FIC1 protein). Patients with PFIC 1 present in the first months of life with severe pruritis, very high bile acids, low cholesterol, and a low or normal GGT. Owing to the extrahepatic expression of ATP8B1, these children may also have severe diarrhea, pancreatitis, or hearing impairment.[57] Antipruritis medications are required, and in cases with intractable pruritis, partial biliary diversion provides some symptomatic relief.[58] PFIC 2 is caused by a defect in the canalicular bile salt excretory pump (BSEP) due to the mutation in ABCB11 gene. Cholestasis is usually permanent from the time of infancy and is associated with severe pruritis, low cholesterol, and a normal or low GGT. There are no extrahepatic manifestations. PFIC 3 can present anytime during childhood or even in an adult. It occurs due to defect in the canalicular phospholipid transporter MDR3 (mutations in ABCB4 gene). GGT is markedly elevated, and pruritis is relatively less.[57] PFIC 4 was recently identified in 12 children who had cholestasis with low GGT, and truncating protein mutations were found in tight junction protein 2 (TJP 2). Cholestasis develops early in infancy, and the disease is progressive.[24] Most patients with PFIC require liver transplant in childhood due to progressive liver disease. For PFIC 2, 3, and 4, LT is curative, but for PFIC 1, the extrahepatic manifestations, especially diarrhea, may worsen after transplant.[59]

12.4. Alagille syndrome

AGS is a multisystem-inherited disorder (autosomal dominant). It occurs due to mutations in either JAG1 (95% cases) or NOTCH 2 (5%) genes and is characterized by paucity of intralobular bile ducts.[60,61] Patients with AGS have a combination of characteristics including chronic cholestasis; characteristic facial features (broad forehead, deep-set eyes, and small pointed chin); skeletal abnormalities such as butterfly vertebrae, curved phalanges, and short ulna; cardiac anomalies (peripheral pulmonic stenosis); and ocular abnormalities such as posterior embryotoxon and optic nerve drusen. Infants present with cholestasis with very high GGT. Liver biopsy shows paucity of intralobular bile ducts (ratio <0.5). On cholangiogram, the extrahepatic biliary tree is patent. The treatment is supportive, and more than half of children progress to cirrhosis requiring liver transplantation by 10 years of age.[62]

12.5. Cholestasis in preterm infants

Cholestasis is commonly seen in preterm babies and occurs due to multiple factors such as immaturity of biliary excretion, perinatal hypoxia, poor enteral feedings, parenteral nutrition (PN, drug toxicity, and sepsis. It has been reported in 18–67% of infants receiving PN for prolonged periods (>14 days).[63] The occurrence of cholestasis due to PN is inversely correlated to the birth weight of the child and directly correlated with starvation or duration of PN.[64,65] Soyabean-based lipid emulsions used commonly in PN are known to have a role in cholestasis due to their phytosterol content which leads to decreased bile secretion and omega-6 fatty acids, which are proinflammatory hepatic agents. Fish oil–based lipid emulsions contain omega-3 fatty acids and seem to be useful in preventing neonatal cholestasis.[66] A lipid emulsion containing a mixture of soy bean oil, medium-chain triglycerides, olive oil and fish oil (SMOF lipid) with reduced omega-6 fatty acids with vitamin E was found to decrease GGT in preterm infants as compared to soy-based lipids.[67] The management of PN-induced cholestasis includes discontinuation of PN as soon as possible and promotion of enteral feeding which enhances gall bladder contraction, bile flow, and intestinal motility.

13. Conclusion

A variety of disorders have neonatal cholestasis as their presentation. Any infant with jaundice after 2 weeks of age should be evaluated for cholestasis. EHBA is one of the most common causes, and it must be differentiated promptly from other intrahepatic causes because early surgery at less than 2 months of age results in a better outcome. Previously underdiagnosed, genetic and metabolic disorders are more readily recognized nowadays because of advanced genetic testing, and many of these disorders have specific treatment as well. Systematic approach helps in early diagnosis and management, thus reducing the complications.

Conflicts of interest

Nothing declared.

References

1. Kelly DA, Stanton A. Jaundice in babies: implications for community screening for biliary atresia. *BMJ*. 1995;310:1172–1173.
2. McKiernan PJ. The infant with prolonged jaundice: investigation and management. *Curr Paediatr*. 2001;11:83–89.
3. De Bruyne R, Van Biervliet S, Vande Velde S, Van Winckel M. Clinical practice: neonatal cholestasis. *Eur J Pediatr*. 2011;170:279–284.
4. Bijl EJ, Bharwani KD, Houwen RH, de Man RA. The long-term outcome of the Kasai operation in patients with biliary atresia: a systematic review. *Neth J Med*. 2013;71:170–173.
5. Dick MC, Mowat AP. Hepatitis syndrome in infancy- an epidemiological survey with 10 year follow up. *Arch Dis Child*. 1985;60:512–516.
6. McKiernan PJ. Neonatal cholestasis. *Semin Neonatol*. 2002;7:153–165.
7. Venigalla S, Gourley GR. Neonatal cholestasis. *Semin Perinatol*. 2004;28:348–355.
8. Feldman AG, Sokol RJ. Neonatal cholestasis. *NeoReviews*. 2013;14:e63.
9. Fawaz R, Baumann U, Ekong U, et al. Guideline for the evaluation of cholestatic jaundice in infants: joint recommendations of the North American society for pediatric Gastroenterology, Hepatology, and nutrition and the European society for pediatric Gastroenterology, Hepatology, and nutrition. *J Pediatr Gastroenterol Nutr*. 2017;64:154–168.
10. Moyer V, Freese DK, Whitington PF, et al. Guideline for the evaluation of cholestatic jaundice in infants: recommendations of the North American society for pediatric Gastroenterology, Hepatology and nutrition. *J Pediatr Gastroenterol Nutr*. 2004;39:115–128.
11. Hay JE. Liver disease in pregnancy. *Hepatology*. 2008;47:1067–1076.
12. Whitington PF. Fetal and infantile hemochromatosis. *Hepatology*. 2006;43:654–660.
13. Chen HW, Chen HL, Ni YH, et al. Chubby face and the biochemical parameters for the early diagnosis of neonatal intrahepatic cholestasis caused by citrin deficiency. *J Pediatr Gastroenterol Nutr*. 2008;47:187–192.
14. Bull LN, Mahmoodi V, Baker AJ, et al. VPS33B mutation with ichthyosis, cholestasis, and renal dysfunction but without arthrogryposis: incomplete ARC syndrome phenotype. *J Pediatr*. 2006;148:269–271.
15. Choi HJ, Lee MW, Choi JH, et al. Ichthyosis associated with ARC syndrome: ARC syndrome is one of the differential diagnoses of ichthyosis. *Pediatr Dermatol*. 2005;22:539–542.
16. Davenport M, Tizzard SA, Underhill J, et al. The biliary atresia splenic malformation syndrome: a 28-year single-center retrospective study. *J Pediatr*. 2006;149:393–400.
17. Ohama K, Nagase H, Ogino K, et al. Alpha-fetoprotein (AFP) levels in normal children. *Eur J Pediatr Surg*. 1997;7:267–269.
18. Treepongkaruna S, Jitraruch S, Kodcharin P, et al. Neonatal intrahepatic cholestasis caused by citrin deficiency: prevalence and *SLC25A13* mutations among Thai infants. *BMC Gastroenterol*. 2012;12:141.
19. Hirfanoglu IM, Unal S, Onal EE, et al. Analysis of serum gammaglutamyl transferase levels in neonatal intensive care unit patients. *J Pediatr Gastroenterol Nutr*. 2014;58:99–101.
20. Davit-Spraul A, Gonzales E, Baussan C, et al. Progressive familial intrahepatic cholestasis. *Orphanet J Rare Dis*. 2009;4:1.
21. Sundaram SS, Bove KE, Lovell MA, et al. Mechanisms of disease: inborn errors of bile acid synthesis. *Nat Clin Pract Gastroenterol Hepatol*. 2008;5:456–468.
22. Lu FT, Wu JF, Hsu HY, et al. γ-Glutamyl transpeptidase level as a screening marker among diverse etiologies of infantile intrahepatic cholestasis. *J Pediatr Gastroenterol Nutr*. 2014;59:695–701.
23. Van Mil SW, Houwen RH, Klomp LW. Genetics of familial intrahepatic cholestasis syndromes. *J Med Genet*. 2005;42:449–463.
24. Sambrotta M, Strautnieks S, Papouli E, et al. Mutations in TJP2 cause progressive cholestatic liver disease. *Nat Genet*. 2014;46:326–328.
25. Wang JS, Tan N, Dhawan A. Significance of low or normal serum gamma glutamyl transferase level in infants with idiopathic neonatal hepatitis. *Eur J Pediatr*. 2006;165:795–801.
26. Maggiore G, Bernard O, Hadchouel M, et al. Diagnostic value of serum gamma-glutamyl transpeptidase activity in liver diseases in children. *J Pediatr Gastroenterol Nutr*. 1991;12:21–26.
27. Balistreri WF. Inborn errors of bile acid biosynthesis and transport—novel forms of metabolic liver disease. *Gastroenterol Clin N Am*. 1999;28:145–172.
28. Balistreri WF. Neonatal cholestasis. *J Pediatr*. 1985;106:171–184.
29. Mittal V, Saxena AK, Sodhi KS, et al. Role of abdominal sonographyin the preoperative diagnosis of extrahepatic biliary atresia in infants younger than 90 days. *AJR Am J Roentgenol*. 2011;196:W438–W445.
30. Humphrey TM, Stringer MD. Biliary atresia: US diagnosis. *Radiology*. 2007;244:845–851.
31. Lee HJ, Lee SM, Park WH, et al. Objective criteria of triangular cord sign in biliary atresia on US scans. *Radiology*. 2003;229:395–400.
32. Kim WS, Cheon JE, Youn BJ, et al. Hepatic arterial diameter measured with US: adjunct for US diagnosis of biliary atresia. *Radiology*. 2007;245:549–555.
33. Aziz S, Wild Y, Rosenthal P, Goldstein RB. Pseudo gallbladder sign in biliary atresia – an imaging pitfall. *Pediatr Radiol*. 2011;41:620–626.
34. Dehghani SM, Haghighat M, Imanieh MH, Geramizadeh B. Comparison of different diagnostic methods in infants with cholestasis. *World J Gastroenterol*. 2006;12:5893–5896.
35. Takamizawa S, Zaima A, Muraji T, et al. Can biliary atresia be diagnosed by ultrasonography alone? *J Pediatr Surg*. 2007;42:2093–2096.
36. Gilmour SM, Hershkop M, Reifen R, Gilday D, Roberts EA. Outcome of hepatobiliary scanning in neonatal hepatitis syndrome. *J Nucl Med*. 1997;38:1279–1282.
37. Esmaili J, Izadyar S, Karegar I, Gholamrezanezhad A. Biliary atresia in infants with prolonged cholestatic jaundice: diagnostic accuracy of hepatobiliary scintigraphy. *Abdom Imag*. 2007;32:243–247.
38. Kianifar HR, Tehranian S, Shojaei P, et al. Accuracy of hepatobiliary scintigraphy for differentiation of neonatal hepatitis from biliary atresia: systematic review and meta-analysis of the literature. *Pediatr Radiol*. 2013;43:905–919.
39. Gilmour SM, Hershkop M, Reifen R, et al. Outcome of hepatobiliary scanning in neonatal hepatitis syndrome. *J Nucl Med*. 1997;38:1279–1282.
40. Majd M, Reba RC, Altman RP. Hepatobiliary scintigraphy with 99mTc-PIPIDA in the evaluation of neonatal jaundice. *Pediatrics*. 1981;67:140–145.
41. Shanmugam NP, Harrison PM, Devlin J, et al. Selective use of endoscopic retrograde cholangiopancreatography in the diagnosis of biliary atresia in infants younger than 100 days. *J Pediatr Gastroenterol Nutr*. 2009;49:435–441.
42. Keil R, Snajdauf J, Rygl M, et al. Diagnostic efficacy of ERCP in cholestatic infants and neonates-a retrospective study on a large series. *Endoscopy*. 2010;42:121–126.
43. Liu B, Cai J, Xu Y, et al. Three-dimensional magnetic resonance cholangiopancreatography for the diagnosis of biliary atresia in infants and neonates. *PLoS One*. 2014;9, e88268.
44. Govender P, Jonas MM, Alomari A, et al. Sonography-guided percutaneous liver biopsies in children. *AJR Am J Roentgenol*. 2013;201:645–650.
45. Zerbini MC, Gallucci SD, Maezono R, et al. Liver biopsy in neonatal cholestasis: a review on statistical grounds. *Mod Pathol*. 1997;10:793–799.
46. Russo P, Magee JC, Boitnott J, et al. Design and validation of the biliary atresia research consortium histologic assessment system for cholestasis in infancy. *Clin Gastroenterol Hepatol*. 2011;9:357–62e2.
47. Azar G, Beneck D, Lane B, et al. Atypical morphologic presentation of biliary atresia and value of serial liver biopsies. *J Pediatr Gastroenterol Nutr*. 2002;34:212–215.
48. Shteyer E, Ramm GA, Xu C, et al. Outcome after portoenterostomy in biliary atresia: pivotal role of degree of liver fibrosis and intensity of stellate cell activation. *J Pediatr Gastroenterol Nutr*. 2006;42:93–99.
49. el-Youssef M, Whitington PF. Diagnostic approach to the child with hepatobiliary disease. *Semin Liver Dis*. 1998;18:195–202.
50. Altman RP, Abramson S. Potential errors in the diagnosis and surgical management of neonatal jaundice. *J Pediatr Surg*. 1985;20:529–534.
51. Chen CY, Tsao PN, Chen HL, Chou HC, Hsieh WS, Chang MH. Ursodeoxycholic acid (UDCA) therapy in very-low-birth-weight infants with parenteral nutrition-associated cholestasis. *J Pediatr*. 2004;145:317–321.
52. McKiernan PJ, Baker AJ, Kelly DA. The frequency and outcome of biliary atresia in the UK and Ireland. *Lancet*. 2000;355:25–29.
53. Schwarz KB, Haber BH, Rosenthal P, et al. Extrahepatic anomalies in infants with biliary atresia: results of a large prospective North American multicenter study. *Hepatology*. 2013;58:1724–1731.
54. Serinet MO, Wildhaber BE, Broué P, et al. Impact of age at Kasai operation on its results in late childhood and adolescence: a rational basis for biliary atresia screening. *Pediatrics*. 2009;123:1280–1286.
55. Hartley J, Davenport M, Kelly D. Biliary atresia. *Lancet*. 2009;374:1704–1713.
56. Duffy J, Kao K, Ko CY, et al. Long-term patient outcome and quality of life after liver transplantation: analysis of 20-year survivors. *Ann Surg*. 2010;252:652–661.
57. Carlton VE, Pawlikowska L, Bull LN. Molecular basis of intrahepatic cholestasis. *Ann Med*. 2004;36:606–617.
58. Kurbegov AC, Setchell KD, Haas JE, et al. Biliary diversion for progressive familial intrahepatic cholestasis: improved liver morphology and bile acid profile. *Gastroenterology*. 2003;125:1227–1234.
59. Jansen PL, Strautnieks SS, Jacquemin E, et al. Hepatocanalicular bile salt export pump deficiency in patients with progressive familial intrahepatic cholestasis. *Gastroenterology*. 1999;117:1370–1379.
60. Li L, Krantz ID, Deng Y, et al. Alagille syndrome is caused by mutations in human Jagged1, which encodes a ligand for Notch1. *Nat Genet*. 1997;16:243–251.
61. McDaniell R, Warthen DM, Sanchez-Lara PA, et al. NOTCH2 mutations cause Alagille syndrome, a heterogeneous disorder of the notch signaling pathway. *Am J Hum Genet*. 2006;79:169–173.
62. Lykavieris P, Hadchouel M, Chardot C, Bernard O. Outcome of liver disease in children with Alagille syndrome: a study of 163 patients. *Gut*. 2001;49:431–435.
63. Javid PJ, Malone FR, Dick AA, et al. A contemporary analysis of parenteral nutrition-associated liver disease in surgical infants. *J Pediatr Surg*. 2011;46:1913–1917.

64. Costa S, Maggio L, Sindico P, Cota F, De Carolis MP, Romagnoli C. Preterm small for gestational age infants are not at higher risk for parenteral nutrition-associated cholestasis. *J Pediatr*. 2010;156:575–579.
65. Christensen RD, Henry E, Wiedmeier SE, Burnett J, Lambert DK. Identifying patients, on the first day of life, at high-risk of developing parenteral nutrition-associated liver disease. *J Perinatol*. 2007;27:284–290.
66. Premkumar MH, Carter BA, Hawthorne KM, King K, Abrams SA. High rates of resolution of cholestasis in parenteral nutrition-associated liver disease with fish oil-based lipid emulsion monotherapy. *J Pediatr*. 2013;162:793–798.
67. Tomsits E, Pataki M, Tölgyesi A, Fekete G, Rischak K, Szollár L. Safety and efficacy of a lipid emulsion containing a mixture of soybean oil, medium-chain triglycerides, olive oil, and fish oil: a randomised, double-blind clinical trial in premature infants requiring parenteral nutrition. *J Pediatr Gastroenterol Nutr*. 2010;51:514–521.