Cholestasis in Infancy

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ABSTRACT

Jaundice is a key manifestation of hepatobiliary disease in all age groups. Jaundice is a common finding in the first 2 weeks after birth, , occurring in 2.4% to 15% of newborns. The neonatal liver is at increased susceptibility to cholestasis, with an incidence ranging from 1 in 2,500 to 1 in 5,000 live births. Etiologies vary, but the most common is biliary atresia. In 2004, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition published guidelines for the evaluation of cholestasis that clearly stated any infant with jaundice persisting beyond age 2 weeks (3 weeks in breast-fed infants with an otherwise normal history and physical examination) should be evaluated with a fractionated serum bilirubin level. Prompt evaluation, diagnosis, and intervention are vital to optimize timely intervention and improve clinical outcomes. This article discusses the etiology, diagnosis and evaluation of cholestatis in infants. **[*Pediatr Ann*. 2016;45(12):e414-e419.]**

Clinical jaundice in the first 2 weeks after birth is a common finding, occurring in 2.4% to 15% of newborns.[1] Often benign, it usually resolves spontaneously by age 2 weeks but may persist for several weeks in the breast-fed infant. Any jaundice beyond age 3 weeks is considered abnormal and requires evaluation with a fractionated serum bilirubin level.[2]

Cholestasis, defined as a decrease in bile formation or flow secondary to hepatocellular or obstructive cholestasis, stems from a variety of etiologies including genetic, metabolic, infectious, and toxin-mediated causes (**Table 1**). Hepatocellular cholestasis occurs secondary to reduced bile formation, such as in idiopathic neonatal hepatitis and infectious hepatitis. On the other hand, obstructive cholestasis is due to either intra- or extrahepatic obstruction, a product of either anatomical or functional obstruction of the biliary system, such as in biliary atresia (BA) and Alagille syndrome.

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Cholestasis is defined as a conjugated/direct hyperbilirubinemia >1 mg/dL if total serum bilirubin is ≤5 mg/dL, or if direct bilirubin fraction is >20% of total bilirubin when the total is >5 mg/dL. Histologically, bile pigment is present in hepatocytes and bile ducts, whereas physiologically the accumulation of substances normally excreted in bile are present in blood and extrahepatic tissues.[3]

BA is the most common cause of cholestasis in the neonatal period, accounting for approximately 20% to 35% of infantile cholestasis cases[4,5] and with a wide range of reported incidence rates worldwide. In the past, idiopathic neonatal hepatitis accounted for the majority of neonatal cholestasis cases, but in the present its histologic finding of giant cell transformation is known to be nonspecific and attributable to multiple infectious, metabolic, and genetic disorders.[5,6] Fewer than 5% of infantile cholestasis cases are secondary to congenital infections.

Immaturity of the neonatal liver in bile synthesis, transport, and metabolism renders it more susceptible to cholestasis. The physiologic development of the hepatic function matures in late gestation and over the first few months after birth. This immaturity contributes to decreased capacity to synthesize and transport bile acids and affects the metabolism, detoxification and excretion of drugs, xenobiotics, and bile.[7,8]

DIFFERENTIAL DIAGNOSIS

Conjugated hyperbilirubinemia portends a hepatobiliary pathology that requires further evaluation in a time-

sensitive manner. More than 95% of neonatal cholestasis cases can be attributed to a small number of disorders, some of which are discussed in the following text[9] (**Table 1**).

Obstructive

The most common forms of obstructive cholestasis in infancy are BA and choledochal cysts. BA is a fibroinflammatory disease of the biliary tree. The etiology of BA is not yet fully known, but it is the most common etiology of chronic cholestasis in infants and children, and is the most common indication for pediatric liver transplantation.[10] Affecting 1 in 8,000 to 12,000 live births worldwide, there are two major types: perinatal/acquired (accounting for more than 80% of cases), and congenital/embryonic cases.[11] Typically, it presents with jaundice and acholic stools in the few-weeks-old thriving infant.

Physical findings, other than icterus, may not be present in the first few weeks of postnatal life, especially in infants with acquired cases. Early detection and timely referral to a pediatric gastroenterologist are crucial because timely surgical intervention with a Kasai hepatoportoenterostomy has the best outcomes if performed between age 45 and 60 days by experienced surgeons.[12-14]

In a Kasai hepatoportoenterostomy, a Roux-en-Y loop of jejunum is anastomosed to the hilum of the liver, creating a conduit for biliary drainage. Patients are usually provided with a high-calorie diet to circumvent malabsorption, especially in the case of an unsuccessful surgical outcome. They are also placed on ursodeoxycholic acid, fat-soluble vitamins, and antibiotic prophylaxis against ascending cholangitis.[10]

Diagnosis and treatment prior to the first 45 to 60 days of postnatal life improves the transplant-free survival rate to upwards of 75% to 90%.[12-14] However, if a Kasai hepatoportoenterostomy fails to clear the cholestasis, the 3-year transplant-free survival rate is only 20%.[9] Total bilirubin levels 3 months post-Kasai hepatoportoenterostomy can indicate the prognosis, with a 2-year survival rate of only 16% with the native liver if the total bilirubin is >6 mg/dL, compared to an 84% rate if the total bilirubin level is <2 mg/dL.[15]

Choledochal cysts are congenital conditions involving cystic dilation of the intra- and/or extrahepatic bile ducts. With type determined by location, these often present with jaundice and are treated surgically within the first year of life. A few cases present outside of first year of life and into adulthood as well.

Hepatocellular

Hepatocellular cholestasis was historically attributed to idiopathic neonatal hepatitis (INH), a prolonged conjugated hyperbilirubinemia with no known etiology. However, in recent years, advanced diagnostic capabilities have made INH a rare diagnosis of exclusion, requiring thorough evaluation for congenitally acquired pathogens (rubella, toxoplasmosis, cytomegalovirus, herpes, human immunodeficiency virus, and syphilis) as well as bacterial infections (gram-negative and gram-positive organisms), as seen in infants with urinary tract infections presenting with jaundice. Once all infectious, genetic, and metabolic (including endocrinopathies) causes have been ruled out, confirmation of the disease is achieved via a liver biopsy that demonstrates widespread transformation of multinucleated giant cells. Most of these cases resolve spontaneously over the course of a few months.

Genetic/Metabolic

Different genetic and metabolic diseases present as neonatal cholestasis, including (but not limited to) Alagille syndrome, alpha-1 antitrypsin (alpha1-AT) deficiency, progressive familial intrahepatic cholestasis (PFIC), galactosemia, tyrosinemia, as well as a variety of other extremely rare metabolic disorders.

TABLE 1.

Causes of Infantile Cholestasis

Obstructive
Biliary atresia
Choledochal cyst
Syndromic and nonsyndromic paucity of interlobular bile ducts
Inspissated bile syndrome
Caroli's disease/congenital hepatic fibrosis
Neonatal sclerosing cholangitis
Idiopathic neonatal hepatitis genetic
Alpha-1-antitrypsin deficiency
Alagille syndrome
Progressive familial intrahepatic cholestasis
Cystic fibrosis
Arthrogryposis-renal dysfunction-cholestasis syndrome
Infectious
Congenital TORCH infection
HIV
Bacterial sepsis
Urinary tract infection
Metabolic
Bile acid synthesis defects
Gestational alloimmune liver disease/ neonatal hemochromatosis
Galactosemia
Hereditary tyrosinemia
Hypothyroidism
Panhypopituitarism
Storage diseases
Toxic
Parenteral nutrition
Drugs

Abbreviation: TORCH, Toxoplasmosis, Other agents, Rubella, Cytomegalovirus, Herpes simplex.

Alagille syndrome. Alagille syndrome is an autosomal dominant, multisystemic disease with variable penetrance. It results from mutations of the *JAG1* or *NOTCH2* genes, which are responsible for encoding cell surface proteins that interact with Notch receptors during embryogenesis.[11] Presentation is widely variable, from completely asymptomatic to having one or more of the following: abnormal facies, chronic cholestasis due to paucity of the interlobular bile ducts, posterior embryotoxon, butterfly-like vertebral arch defects, and cardiovascular malformations. Patients are also at increased risk for vascular malformations intrahepatically and cerebrovascularly, creating a condition similar to moyamoya disease. In infants, the presentation and progression varies, with some patients improving with age and others gradually developing cirrhosis. Diet supplementation with medium chain triglycerides, essential fatty acids, and fat-soluble vitamins is emphasized. In extreme cases of cirrhosis, portal hypertension, or severe pruritus, liver transplantation may be indicated.[16]

Alpha-1 antirypsin deficiency. Alpha1-AT deficiency, an autosomal recessive condition that occurs in 1 in 1,600 to 2,000 live births, is extremely rare in the nonwhite population.[11] It results from the intracellular hepatic accumulation of a misfolded alpha1-AT protein, leading to liver injury.[17] Diagnosis is based on the serum levels of alpha1-AT and the phenotype. The normal phenotype is MM; carriers of the mutant Z allele can either be homozygous and thus at risk for liver disease and emphysema, or heterozygous and at risk for liver disease. Neonatal cholestasis is the typical presentation; however, it is highly variable given that <10% of people born with the homozygous Z allele develop any clinically significant liver disease. Two studies indicate that 80% of patients presenting with neonatal cholestasis found to be homozygous for the Z allele are healthy and free of chronic disease by age 18 years.[18] Cirrhosis, portal hypertension, and hepatocellular carcinoma are other hepatic manifestations in older patients.

Progressive familial intrahepatic cholestasis. PFIC is a heterogeneous condition associated with the disruption of bile formation.[19] It is divided into three subtypes, all of which may have a severe presentation in the first year of life.

PFIC type I, known as Byler or familial intrahepatic cholestasis type 1 (FIC1) disease, is associated with a mutation in the P-type adenosine triphosphate (ATP)ase FIC gene. *FIC1* is expressed in several epithelial tissues, including the small intestine, pancreas, and liver. It is responsible for both intra- and extrahepatic manifestations of the disease, such as recurrent pancreatitis, diarrhea, cough, wheeze, sensorineural hearing loss, and posttransplant steatosis.[11] Patients usually present with recurrent cholestasis, which will progress to cirrhosis if left untreated. Less severe disease can present in adulthood.

PFIC type II is caused by a defect in the *ABCB11* gene, which is the gene that encodes the bile salt export pump protein. The defect leads to impaired bile acid transport from the hepatocytes into the bile canaliculi. The gene is liver-specific, and the clinical presentation is similar to that of PFIC type I, although the cholestasis is nonrelapsing, severe, and progressive. Patients usually suffer from severe pruritus, rickets, growth retardation, and early development of cirrhosis. They are at high risk for early development of hepatocellular carcinoma. Both PFIC types I and II are characterized by low-to-normal serum gamma-glutamyl transpeptidase (gamma-GTP) levels, unlike PFIC type III.

PFIC type III results from a defect in the *MDR3* gene, a member of the ATP-binding cassette family of transporters that serves as a phospholipid flippase. This leads to defective biliary phospholipid secretion, impairing the balance of the cholesterol saturation index, leading to crystallization of cholesterol and lithogenicity of bile, which ultimately results in bile duct injury.[11] Presentation in the neonate is rare, and the spectrum of hepatic manifestations includes cholesterol cholelithiasis, intrahepatic cholestasis of pregnancy, and biliary cirrhosis in childhood or adulthood.

Galactosemia. Galactosemia is an inborn error of metabolism that results in liver disease. It is an autosomal recessive disorder resulting in the inability to digest galactose. It results from deficiency of three different enzymes. The most common and severe type of the disorder is due to the absence of galactose-1-phosphate uridyltransferase (GALT). The typical presentation includes jaundice, lethargy, hypotonia, poor feeding, and hepatomegaly. The diagnosis is confirmed by a deficiency or complete absence of GALT activity in red blood cells. Of note, receipt of a blood transfusion prior to newborn screen may alter results and prevent timely diagnosis.[11] Although dietary restriction of galactose can reverse the hepatic dysfunction, chronic and progressive neurologic impairments and infertility may occur in patients despite lifelong dietary compliance.[20]

Tyrosinemia. Tyrosinemia is another inborn error of metabolism in the tyrosine catabolism pathway, most commonly due to fumarylacetoacetate hydrolase deficiency, which results in the accumulation of toxic metabolites such as succinylacetone. It is characterized by acute liver failure and severe renal tubular dysfunction that present in the first

weeks or months of life. It can also present as a chronic liver disease. Evaluation includes quantitative measurement of plasma amino acids and urine succinylacetone levels. Dietary restriction of tyrosine and phenylalanine, as well as early initiation of nitosine, a potent inhibitor of the enzyme 4-hydroxyphenylpyruvate dioxygenase, is the mainstay of treatment.

It is important to remember that the conditions described above are not an exhaustive list and numerous other inborn errors of metabolism may result in neonatal cholestasis.

EVALUATION

It is imperative to distinguish between jaundice caused by direct/conjugated hyperbilirubinemia from indirect/unconjugated hyperbilirubinemia. In 2004, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition published guidelines for the evaluation of cholestasis in infants.[2] They recommended that any infant noted to be jaundiced at age 2 weeks should be evaluated for cholestasis with measurement of total and direct serum bilirubin. The guidelines did, however, make a distinction that breast-fed infants with an otherwise normal history (no dark urine or light stools) and unremarkable physical examination should be seen again at age 3 weeks for further evaluation; if the jaundice persists beyond age 3 weeks, these infants also require evaluation.[2] Multiple studies have supported that early diagnosis, despite the etiology, will lead to better clinical outcomes, especially in cases of BA.[12-14]

Figure 1 is algorithm for the evaluation of infants with cholestasis. A thorough history and physical examination can help guide the preliminary steps of the diagnostic process. For example, acholic stools and dark urine are indicators of cholestasis. A study in Taiwan suggested that providing parents with a stool card as a means of "mass screening" was efficacious in the early diagnosis of BA.[21] Parents may report a history of easy bleeding or bruising that could be due to a coagulopathy from vitamin K malabsorption and/or liver failure. A complete family history may reveal consanguinity or an inherited genetic disorder. A thorough obstetrical history will identify congenital infections, anatomic abnormalities detected in prenatal ultrasounds, and ABO blood group incompatibility, which, in about 3% of infants, results in intrahepatic cholestasis that resolves spontaneously within 1 month.[22]

Additionally, a complete physical examination may reveal identifying clinical features. Population studies[3] have shown BA to be more common in female infants of normal birth weight compared with idiopathic neonatal hepatitis, which is more common in low-birth weight or premature male infants. Alagille syndrome can present with both abnormal facies as well as a cardiac murmur. Congenital BA may be associated with structural heart disease, situs inversus, or dextrocardia besides other intra-abdominal anomalies that radiologic evaluation will reveal. Splenomegaly may be found in patients with portal hypertension, storage disorders, or hemolytic diseases.[11]

Infants with cholestasis in the setting of sepsis, metabolic diseases, or congenital infection usually appear sickly. Congenitally infected newborns are usually small for their gestational age and may have microcephaly, purpuric rash, or chorioretinitis.[11]

Confirmation of cholestasis with an elevated fractionated serum bilirubin level requires a concurrent baseline assessment of hepatic function (serum albumin, glucose, prothrombin time/international normalized ratio (INR), with or without ammonia) to determine the next step in evaluation.

Of note, parenteral administration of vitamin K is recommended in the setting of prolonged INR and should normalize coagulation studies if the synthetic hepatic function is preserved. Serum transaminases (alanine aminotransferase, aspartate aminotransferase) are also indicative of hepatocellular injury but lack prognostic value.

Although the elevation in alkaline phosphatase can be indicative of biliary obstruction, it is nonspecific because it is also produced by bone, small bowel, and kidneys. Unlike alkaline phosphatase, gamma-GTP is more sensitive in identifying biliary disease. Low levels of gamma-GTP in the setting of cholestasis suggest a short list of hepatobiliary diseases, including PFIC type I, PFIC type II, arthrogryposis-renal dysfunction-cholestasis syndrome (ARC), and inborn errors of bile acid synthesis (**Table 2**).[11]

Metabolic acidosis on an electrolyte panel or blood gas sample could indicate a metabolic disease, especially in the setting of other abnormalities such as hypoglycemia, hyperammonemia, and lactic acidosis with or without ketonuria.

Alpha1-AT level and phenotype need to be checked early in the diagnostic process, as the histologic differentiation between BA and alpha1-AT deficiency is very difficult in neonates.[11]

Blood and urine cultures should be drawn when clinically indicated. Septicemia leads to downregulation of biliary transporters, biliary stasis, and hepatic parenchymal injury from circulating endotoxins.

RADIOLOGY EVALUATION

Ultrasonography is the initial imaging study of choice to assess hepatic size, echogenicity, and anatomic anom-

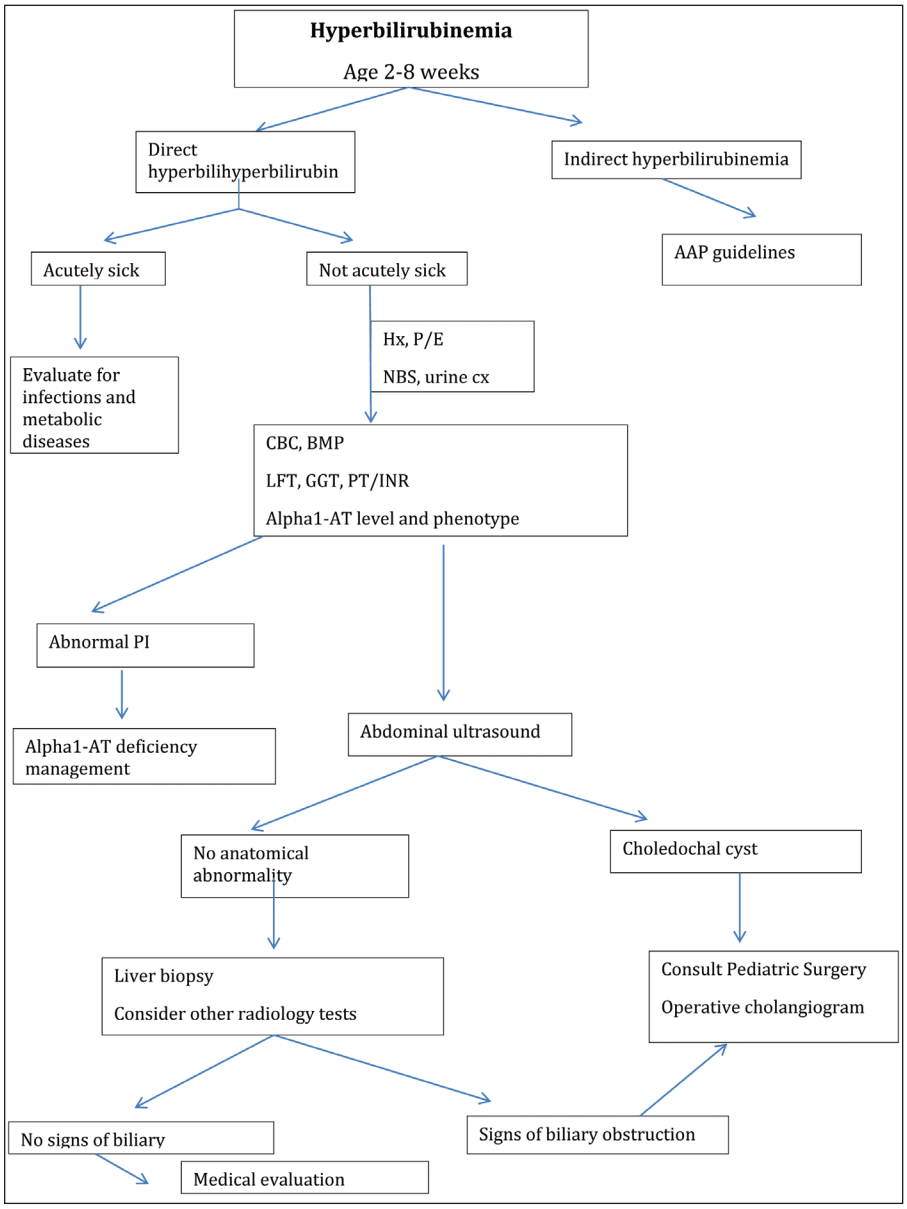

Figure 1. An algorithm for the evaluation of infants with cholestasis. AAP, American Academy of Pediatrics; A1-AT, alpha1-antitrypsin; BMP, basic metabolic profile; CBC, complete blood count; cx, culture; GGT, gamma-glutamyl transferase; Hx, history; LFT, liver function test; NBS, newborn screen; P/E, physical examination; PT/INR, prothrombin time/international normalized ratio; PI, phenotype. Adapted from Young and Azzam.[11]

TABLE 2.

Causes of Cholestasis with Low or Normal Gamma GTP

PFIC type I
PFIC type II
Inborn errors of bile acid synthesis
Arthrogryposis–renal dysfunction–cholestasis
Lymphedema cholestasis (Aegenaes syndrome)

Abbreviations: GTP, glutamyltranspeptidase; PFIC, progressive familial intrahepatic cholestasis.

alies of the liver. It also assesses the presence and size of the gall bladder, biliary stones, or sludge. Ultrasound can identify signs of obstruction or dilatation of the biliary tree, extrahepatic anomalies such as polysplenia, asplenia, or situs inversus, as well as the different positional variants of the portal vein and hepatic artery.[11] Signs of BA include a small or absent gallbladder as well as a "triangular cord sign" or triangular echogenicity of the anterior wall of the right portal vein on transverse or longitudinal view.[3] Although the use of ultrasound is limited by operator dependence, it is still recommended over computed tomography, which delivers significant radiation.

Magnetic resonance cholangiography (MRCP) performed with T2-weighted turbo spin-echo sequences is noninvasive and not operator dependent; however, it does require sedation.[11] MRCP can evaluate structural anomalies in detail. The addition of gadolinium enhancement for its T2-shortening effect may allow for a more definitive determination of the presence or absence of the common bile duct in infants with cholestasis, especially when conventional MRCP is inconclusive.[21]

The ability to differentiate extrahepatic biliary obstruction from nonobstructive causes has been done with hepatobiliaryscintigraphy using technetium-99m iminodiacetic acid analogues. The addition of phenobarbital for 3 to 5 days before the test increases its yield but may delay the time to diagnosis.[11]

Endoscopic retrograde cholangiography (ERCP) is also considered a safe and reliable diagnostic method in infants with cholestasis. Its sensitivity and specificity in the diagnosis of extrahepatic causes of cholestasis is superior to other available diagnostic methods when performed by a skilled and experienced endoscopist.[11] In the case of BA

and choledochal cysts, the high negative-predictive value and specificity of ERCP is superior to other radiologic modalities in diagnosing structural abnormalities of the bile ducts.[23]

Along with blood testing and radiographic evaluation, liver biopsy remains an important diagnostic tool, with accuracy reported as high as 90% to 95% in BA.[3] Timing is important, as tests performed prematurely will not demonstrate the typical histopathologic features of BA, requiring serial investigations and repeat biopsy at age 6 weeks. Liver biopsy can also be diagnostic of other conditions via electron microscopy, or immunohistochemical or biochemical staining.

The final and most invasive means of imaging is an intraoperative cholangiogram, the gold standard test to study the patency of the biliary system. This test establishes the diagnosis of BA and is often chosen by surgeons when the diagnosis remains elusive despite imaging studies and liver biopsy.[11]

CONCLUSION

Although the causes of neonatal cholestasis can be many (some of which are benign), prompt and thorough evaluation is always indicated to avoid devastating outcomes.

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