Updates in Diagnosis and Management of Neonatal Cholestasis

Abstract:

Neonatal jaundice refers to the yellow coloration of the skin and sclera of newborn babies that results from hyperbilirubinemia. About 50% of term and 80% of preterm babies develop jaundice in the first week of life. Jaundice is also a common cause of re-admission to hospital after early discharge of newborn babies. Jaundice tends to develop because of two factors—the breakdown of fetal hemoglobin as it is replaced with adult hemoglobin and the relatively immature metabolic pathways of the liver, which are unable to conjugate and so excrete bilirubin as quickly as an adult. This causes an accumulation of bilirubin in the blood (hyperbilirubinemia), leading to the symptoms of jaundice. The typical findings in an infant who has cholestasis are protracted jaundice, scleral icterus, acholic stools, dark yellow urine, and hepatomegaly.Evaluation of a jaundiced infant should begin with fractionation of serum bilirubin into total and direct (or conjugated) bilirubin. Phototherapy is started based on risk factors and the serum bilirubin level on the nomogram, IV immunoglobulin is recommended for increasing bilirubin levels from iso-immune hemolysis despite phototherapyand exchange transfusion is indicated if there is a risk of neurologic dysfunction with or without an attempt at phototherapy.

Key words: Neonatal jaundice, hyperbilirubinemia, cholestasis. Icterus.

Introduction:

Neonatal jaundice/ cholestasis refers to the yellow coloration of the skin and sclera of newborn babies that results from hyperbilirubinemia. A yellowish discoloration of the skin, sclera, mucous membranes, and bodily fluids, are the commonest clinical finding in the first 2 weeks after birth, occurring in 2.4% to 15% of newborns. Most often, jaundice is of the indirect/ unconjugated bilirubin variety and resolves spontaneously without

intervention. However, persistent jaundice is abnormal and can be the presenting sign of serious hepatobiliary and metabolic dysfunction. (1)

Cholestasis represents an impairment in bile flow and may be caused by either an intrahepatic or extrahepatic disorder. To differentiate cholestasis from benign causes of jaundice, the serum bilirubin must be fractionated into conjugated and unconjugated fractions. When jaundice persists beyond age 2 weeks, cholestasis or conjugated hyperbilirubinemia must be considered in the differential diagnosis. (2)

Any infant who remains jaundiced beyond age 2 to 3 weeks needs to be evaluated to first exclude neonatal cholestasis and, if present, to rapidly identify those causes of cholestasis that are amenable to medical or surgical treatment. Even when specific treatment is not available or curative, infants who have cholestasis benefit from early medical management and optimization of nutrition to prevent complications. (3) Imaging studies like ultrasonography and additional tests like TORCH titers, urine culture, viral cultures, serologic titers, amino acids, and the a-antitrypsin phenotype may be added depending on the suspected diagnosis for conjugated hyperbilirubinemia. (4) Despite data showing that early diagnosis of cholestasis and its etiologies is potentially life-saving, delayed diagnosis remains a problem. Early hospital discharge of newborns, inadequate follow-up of persisting jaundice, false reassurance by the appearance of pigmented stool, fluctuating serum bilirubin levels, and misdiagnosis of human milk–associated jaundice are all cited as reasons for late referral for evaluation of cholestasis. The need for treatment depends on bilirubin levels, the age of the child, and the underlying cause. Treatments may include more frequent feeding, phototherapy, or exchange transfusions. (5)

Epidemiology:

Jaundice is the most common condition requiring medical attention in newborn babies. About 50% of term and 80% of preterm babies develop jaundice in the first week of

life. Jaundice is also a common cause of re-admission to hospital after early discharge of newborn babies. Jaundice usually appears 2 to 4 days after birth and disappears 1 to 2 weeks later, usually without the need for treatment. (6)

Etiology:

In newborns, jaundice tends to develop because of two factors—the breakdown of fetal hemoglobin as it is replaced with adult hemoglobin and the relatively immature metabolic pathways of the liver, which are unable to conjugate and so excrete bilirubin as quickly as an adult. This causes an accumulation of bilirubin in the blood (hyperbilirubinemia), leading to the symptoms of jaundice. Over 75% of neonatal unconjugated hyperbilirubinemia is due to physiologic causes. (7) Physiologic jaundice is also referred to as non-pathologic jaundice, and it is mild and transient. This occurs because of differences in the metabolism of bilirubin in the neonatal period leading to an increased bilirubin load. The increased bilirubin load in the newborn arises from increased production of bilirubin due to a higher mass of red blood cells with a reduced lifespan in the neonate, a decreased bilirubin clearance from a deficiency of the uridine diphosphate glucuronosyltransferase (UGT) enzyme, which in the newborn has the activity of about 1% of the adult liver, and increased enterohepatic circulation. (8)

Physiologic jaundice usually occurs on days 2 to 4, peaks between 4 to 5 days, and resolves in 2two weeks. Physiologic jaundice never occurs in the first 24 hours. (9)

Similarly, the causes of pathologic unconjugated hyperbilirubinemia are also due to increased bilirubin production, decreased bilirubin clearance, and increased enterohepatic circulation. Pathologic jaundice may occur in the first 24 hours of life and is characterized by a rapid rate of rising in the bilirubin level more than 0.2 mg/dl per hour or 5 mg/dl per day. (10)

Causes of increased bilirubin production in pathologic jaundice are immune-mediated hemolysis such as ABO and Rhesus incompatibility, non-immune mediated causes such

as cephalhematoma, red blood cell membrane defects like hereditary spherocytosis and elliptocytosis, enzyme defects like glucose-6-phosphate dehydrogenase (G6PD) deficiency and pyruvate kinase. (11)

The G6PD enzyme, found in red blood cells (RBCs), protects against oxidative injury by the production of NADPH from NADP. With its deficiency, and in the presence of oxidant stressors like illness, certain drugs, dyes, and foods like fava beans, there is hemolysis of RBCs. (12)

ABO incompatibility occurs in mothers with blood group O who have anti-A and anti-B IgG antibodies that cross the placenta and cause hemolysis in newborns with blood group A or B. In Rhesus (Rh) incompatibility. (13)

Decreased bilirubin clearance occurs in inherited disorders such as Crigler-Najjar and Gilbert syndrome, as well as maternal diabetes and congenital hypothyroidism.

Biliary atresia is the most common cause of conjugated neonatal hyperbilirubinemia. It involves both intra-hepatic and extra-hepatic bile ducts and classically presents around 2 to 4 weeks of life with pale stools. The initial evaluation is by ultrasonography that may show an absent gallbladder and the classic "triangular cord" sign. (14)

Alpha-1-antitrypsin deficiency is a common genetic disorder that presents with cholestatic jaundice in infants who are homozygous for the PiZZ genotype. Accumulation of anti-trypsin polymers in hepatocytes of a patient with the PiZZ genotype leads to apoptosis, neonatal cholestasis, and cirrhosis later in childhood.

Clinical Picture:

The typical findings in an infant who has cholestasis are protracted jaundice, scleral icterus, acholic stools, dark yellow urine, and hepatomegaly. It should be noted that there may be a perception of decreasing jaundice over the first weeks after birth as the indirect bilirubin component (from human milk–associated jaundice) decreases, causing

false reassurance that the jaundice is resolving and need not be evaluated further. (15) An infant may likewise present with bleeding diathesis; pruritis; deficiency of vitamins A, D, E, K; and failure to thrive. Besides these general symptoms, there are specific clinical features depending on the cause. Coagulopathy may be caused by vitamin K deficiency, liver failure, or severe metabolic derangement of the liver (as in neonatal hemochromatosis). (16) Splenomegaly can be seen. Neurologic abnormalities including irritability, lethargy, poor feeding, or seizures can indicate sepsis, intracranial hemorrhage, metabolic (including Zellweger syndrome) and mitochondrial disorders, or severe liver dysfunction resulting in hyperammonemia and encephalopathy. A cardiac murmur increases the likelihood of Alagille syndrome or biliary atresia. Low birth weight, petechiae and purpura, and chorioretinitis are regularly associated with intrauterine infections. Facial dysmorphism may suggest a chromosomal abnormality. An obvious mass in the upper quadrant of the abdomen may indicate a choledochal cyst. (17) On physical examination, infants with biliary atresia are generally thriving well and are appearing well except for jaundice, and stools are often acholic. However, biliary atresia may present with features of advanced liver disease such as ascites and hepatosplenomegaly if there is a delay in diagnosis. A peculiar odor of body or urine may point to a metabolic cause. Examination of male genitalia and ability to fix and follow a moving object may be useful clues for panhypopituitarism and septo-optic dysplasia, respectively. (18)

Evaluation:

The American Academy of Pediatrics recommends universal screening with TSB or transcutaneous bilirubin (TcB) levels, or targeted screening based on risk factors. Universal TSB/TcB screening can accurately identify infants whose TSB level is likely to exceed the 95th percentile for age. Some studies have found that the use of risk scores is as accurate as universal screening for predicting hyperbilirubinemia. A

combination of universal screening and risk factor scoring seems to be the most effective method for identifying infants at risk of hyperbilirubinemia. (19)

Evaluation of a jaundiced infant should begin with fractionation of serum bilirubin into total and direct (or conjugated) bilirubin. Infants who have cholestasis will generally have a direct bilirubin greater than 2.0 mg/dL, which will be more than 20% of the total bilirubin concentration. Recent data suggest that in the first 4 days after birth, the cutoff for elevated direct bilirubin may be greater than 0.8 mg/dL and more than 8% to 10% of the total bilirubin. (20)

If cholestasis is present, further evaluation should be completed with a sense of urgency because patients who have BA have a better outcome if they undergo a Kasai hepatic portoenterostomy (HPE) before age 30 to 45 days, and other conditions (e.g., hypothyroidism) require prompt treatment. Levels of liver enzymes, including alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, are usually elevated in a cholestatic infant but are poor predictors of etiology. (21)

Depending on the clinical scenario, bacterial cultures from blood and urine may be indicated. The search for congenital viral infection may include a combination of cultures and serologies; immunoglobulin G–based serologies indicate transplacental transport of maternal immunoglobulin G rather than neonatal infection. (22) The newborn screen can be helpful in identifying galactosemia and hypothyroidism, two treatable causes of cholestasis. An elevated immunoreactive trypsinogen on the newborn screen raises suspicion for cystic fibrosis and should be followed up with genetic testing and/or a sweat test to determine if the infant has cystic fibrosis. A low serum A_1AT level and an abnormal protease inhibitor phenotype (PIZZ and PISZ) are used to identify A_1AT deficiency. (23)

Genetic testing for Alagille syndrome, cystic fibrosis, A_1AT deficiency, three distinct forms of PFIC, and peroxisomal defects are commercially available. In the near future, next-generation DNA sequencing will allow for multiple genetic tests on small amounts of blood at a relatively low cost. (24)

Other tests that are commonly used to establish a specific diagnosis include urine succinylacetone (for hereditary tyrosinemia), sweat test (for cystic fibrosis), thyroid-stimulating hormone and thyroxine (for hypothyroidism), total serum bile acid level and urine bile acid profile (for disorders of bile acid synthesis), and other metabolic diseases), very long chain fatty acid levels (for peroxisomal disorders), and other infectious agent serologies as indicated. (25)

An abdominal ultrasound examination should be obtained as part of the early evaluation of a cholestatic infant to assess liver structure, size, and composition; to evaluate for the presence of ascites; and to identify findings of an extrahepatic obstructive lesion (choledochal cyst, mass, gallstone, and sludge). Ultrasound can also detect polysplenia or asplenia, interrupted inferior vena cava, preduodenal portal vein, and situs inversus. (26)

If a cardiac murmur is appreciated on physical examination, an echocardiogram should be obtained to assess for cardiac anomalies. A chest radiograph may reveal cardiomegaly or butterfly vertebrae in patients who have Alagille syndrome. A careful slit-lamp examination may reveal posterior embryotoxon or other anterior chamber abnormalities in an infant who has Alagille syndrome or chorioretinitis in an infant who has a congenital infection. (27)

Hepatobiliary scintigraphy with a technetium-labeled iminodiacetic acid analogue can sometimes be of assistance in distinguishing obstructive from no obstructive causes of cholestasis. Pretreatment with phenobarbital may increase test sensitivity. Many centers do not routinely use this test in the evaluation of cholestatic infants because it may delay the diagnostic evaluation without providing definitive diagnostic information. At this time, endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography are of limited usefulness for the evaluation of neonatal cholestasis. (28)

Percutaneous liver biopsy remains an important diagnostic tool in evaluating neonatal cholestasis and can be performed safely in even the smallest infants. In several single-

center studies, a diagnosis of BA was correctly suggested by liver biopsy histologic findings in 90% to 95% of cases. A more recent study suggests a somewhat lower predictive value of liver biopsy findings when examined in a multicenter research network. Characteristic histologic findings of BA include bile plugs in the portal tract bile duct, bile ductular proliferation, and portal tract edema and fibrosis. (29)Results of a liver biopsy can be helpful in establishing other causes of neonatal cholestasis, including A1AT deficiency (periodic acid Schiff-positive, diastase-resistant intrahepatocytic globules), Alagille syndrome (bile duct paucity), neonatal sclerosing cholangitis (necroin-flammatory duct lesions), viral infection (cytomegalovirus or herpes simplex virus inclusions), metabolic liver diseases (steatosis and pseudoacinar formation of hepatocytes), PFIC and storage diseases (electron microscopy findings), and INH (multinuclear giant cells, extramedullary hemato-poiesis, and hepatocellular cholestasis). Liver histologic findings in PNAC may resemble all the features of BA and are not useful in differentiating between the two conditions. Repeat liver biopsies may occasionally be needed if the diagnosis is unclear; several of these diseases are dynamic and may not be diagnosable by using results of liver biopsy if performed early in the disease course. (30)

In cases in which BA, choledochal cyst, or biliary tract stone disease is suspected, the infant should undergo intraoperative cholangiography through a mini-laparotomy to delineate the biliary anatomy and localize the area of obstruction. The surgeon should be prepared and capable of performing an HPE for BA or choledochal cyst-corrective surgery during the same surgical session if these lesions are found on cholangiography. The decision to pursue cholangiography in infants who have SBS with suspected PNAC but who develop acholic stools may be difficult and requires careful consideration of the surgical options if BA is found. (31)

Management:

To prevent acute bilirubin encephalopathy and kernicterus, severe hyperbilirubinemia is treated with phototherapy, IV immunoglobulin, or exchange transfusion. There are nomograms available to determine bilirubin levels at which phototherapy and exchange transfusion are indicated. (32)

Phototherapy is started based on risk factors and the serum bilirubin level on the nomogram. Bilirubin absorbs light optimally in the blue-green range (460 to 490 nm) and is either photoisomerized and excreted in the bile or converted into lumirubin and excreted in the urine. During phototherapy, the eyes of the newborn must be covered, and the maximum body surface area exposed to the light. (33) It is important to maintain hydration and urine output as most bilirubin is excreted in the urine as lumirubin. The use of phototherapy is not indicated in conjugated hyperbilirubinemia and may lead to the “bronze baby syndrome” with grayish-brown discoloration of the skin, serum, and urine. After phototherapy is discontinued, there is an increase in the total serum bilirubin level known as the" rebound bilirubin." The "rebound bilirubin" level is usually lower than the level at the initiation of phototherapy and does not require reinitiation of phototherapy. (34)

IV immunoglobulin is recommended for increasing bilirubin levels from iso-immune hemolysis despite phototherapy. IV immunoglobin is initiated when the bilirubin level is within 2 to 3 mg/dl of the exchange transfusion level. (35) Exchange transfusion is indicated if there is a risk of neurologic dysfunction with or without an attempt at phototherapy. It is used to remove bilirubin from the circulation, and in iso-immune hemolysis, it removes circulating antibodies and sensitized red blood cells. Exchange transfusions should take place in the training of the neonatal or pediatric intensive care unit (NICU/ PICU) by trained personnel. A double volume exchange blood transfusion (160 to 180 ml/kg) is performed, replacing the neonate’s blood in aliquots with crossed-matched blood. Complications that may arise from exchange transfusion are electrolyte abnormalities like hypocalcemia and hyperkalemia, cardiac arrhythmias,

thrombocytopenia, blood-borne infections, portal vein thrombosis, graft versus host disease, and necrotizing enterocolitis (NEC). (36)

Phototherapy should resume after exchange transfusion until the bilirubin reaches a level where it can be safely discontinued. (37)

Conclusion:

The typical findings in an infant who has cholestasis are protracted jaundice, scleral icterus, acholic stools, dark yellow urine, and hepatomegaly. Evaluation of a jaundiced infant should begin with fractionation of serum bilirubin into total and direct (or conjugated) bilirubin. Phototherapy is started based on risk factors and the serum bilirubin level on the nomogram, IV immunoglobulin is recommended for increasing bilirubin levels from iso-immune hemolysis despite phototherapy and exchange transfusion is indicated if there is a risk of neurologic dysfunction with or without an attempt at phototherapy.

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