Conjugated Hyperbilirubinemia: Screening and Treatment in Older Infants and Children
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Conjugated Hyperbilirubinemia: Screening and Treatment in Older Infants and Children

Rula Harb, MD,* Daniel W. Thomas, MD†

Introduction
Jaundice refers to yellow discoloration of the skin, sclera, mucous membranes, and body fluids. It is a common problem that can be the presenting sign for many disorders. The challenge for the physician is to identify patients who need additional evaluation. The differential diagnosis for jaundice is age-specific; this review addresses the causative conditions in infants beyond the newborn period, older children, and adolescents.

Jaundice is caused by elevated serum bilirubin concentrations. It is apparent in infants when the serum bilirubin value is greater than 4 to 5 mg/dL (68.4 to 85.5 mcmol/L) and in older children at values greater than 2 to 3 mg/dL (34.2 to 51.3 mmol/L). Serum total bilirubin is measured in the laboratory as the sum of two components: unconjugated (“indirect”) and conjugated (“direct”) fractions. The terms “direct” and conjugated hyperbilirubinemia often are used interchangeably. However, this usage is not always accurate because direct bilirubin may include both the conjugated fraction and bilirubin bound to albumin (delta bilirubin). Delta bilirubin is formed by covalent bonding between conjugated bilirubin in the serum and albumin; it is metabolized with albumin and has a similar half-life of 21 days. The presence of delta bilirubin often prolongs direct hyperbilirubinemia while results of the other liver tests are normalizing. Many hospitals continue to measure direct bilirubin by a method that includes both direct and delta bilirubin. Clinicians should consider asking for a breakdown of the direct bilirubin fraction if the jaundice is prolonged or presenting atypically.

Conjugated hyperbilirubinemia is defined as a conjugated bilirubin concentration greater than 2 mg/dL (34.2 mmol/L) or more than 20% of total bilirubin. It is the biochemical marker of cholestasis used most commonly and defined as perturbation of bile flow. Although jaundice is seen commonly in newborns who have physiologic jaundice, breastfeeding and breast milk jaundice, red blood cell defects, and hemolysis, these are conditions of unconjugated (indirect) hyperbilirubinemia. Causes of unconjugated hyperbilirubinemia in the older infant/child are not reviewed in this article. Conjugated hyperbilirubinemia is less common, affecting approximately 1 in 2,500 infants. This condition is never normal at any age, and distinguishing cholestasis from noncholestatic causes of jaundice is crucial. Prolonged hyperbilirubinemia of greater than 2 to 3 weeks' duration requires additional investigation.

Bilirubin Metabolism
The liver has many functions, many of which depend on its ability to secrete bile. Bile secretion is the method by which the liver excretes toxins, modulates cholesterol metabolism, and aids in the intestinal digestion and absorption of lipids and fat-soluble vitamins. Bile is composed of water, bile acids (cholic and chenodeoxycholic acids), phospholipids, cholesterol, bile pigment (bilirubin), electrolytes, xenobiotics, and metabolized drugs. Impairment of bile flow or secretion by the liver results in backup...
Bilirubin is the product of heme breakdown in the reticuloendothelial cells of the spleen and liver (Fig. 1). The end product of this metabolic pathway is water-insoluble unconjugated bilirubin, which is bound to albumin in the circulation. Unconjugated bilirubin is taken up and metabolized in the liver to conjugated bilirubin (Fig. 2). Conjugated bilirubin is secreted into the biliary system by a specific transporter. Defects in bilirubin conjugation cause unconjugated hyperbilirubinemia (Gilbert syndrome and Crigler-Najjar syndromes I and II). Hepatocellular disease can cause a mixed unconjugated and conjugated hyperbilirubinemia due to both impaired bilirubin conjugation and canalicular excretion. Defects in conjugated bilirubin excretion cause isolated conjugated hyperbilirubinemia without cholestasis (Rotor and Dubin-Johnson syndromes). Other mutations in membrane transporters of other organic anions, such as bile acids, are linked with several diseases, including cystic fibrosis, adrenoleukodystrophy, and the familial intrahepatic cholestasis syndromes.

Once bile is excreted from the liver, it is stored in the gallbladder until a meal activates duodenal cholecystokinin release and expulsion of gallbladder contents into the intestine. Conjugated bilirubin cannot be reabsorbed by intestinal epithelial cells and is degraded by intestinal flora into stercobilin and urobilinogen, which are excreted into stool. A small portion of conjugated bilirubin is deconjugated by intestinal beta-glucuronidase. The unconjugated bilirubin can be reabsorbed into the circulation and returned to the liver, which is known as enterohepatic bilirubin circulation. The amount of bilirubin reabsorbed normally is very small, but it can become significant in cases of bowel obstruction, where relatively more bilirubin is deconjugated and absorbed, thereby increasing serum bilirubin concentrations and worsening jaundice.

**Jaundice in the Infant**

Prolonged jaundice in the infant (lasting beyond 2 to 3 weeks after birth) is abnormal and requires additional investigation. It is paramount to fractionate the bilirubin in infants who have abnormal or prolonged jaundice to identify those who have conjugated hyperbilirubinemia and recognize the disorders that may be amenable to early medical intervention (eg, galactosemia, urinary tract infection) or surgery (eg, biliary atresia, choledochal cyst). In addition, early diagnosis facilitates the institution of necessary nutritional and medical support to promote optimal growth and development.

The causes of cholestatic jaundice in the infant vary and can be divided into two primary categories: obstructive and hepatocellular. A detailed classification is listed in Table 1. The four most common causes of persistent cholestatic jaundice in infants are discussed.

**Extrahepatic Biliary Atresia (EHBA)**

EHBA is the most common and serious cause of prolonged cholestatic jaundice in infants. It results from a progressive and destructive inflammatory process that affects both the extra- and intrahepatic biliary tree. The cause of EHBA has not been identified clearly. Two clinical forms have been defined: an embryonic/fetal form, which constitutes 20% of cases, and a perinatal/acquired type, which comprises the remaining 80% of cases. (1) The embryonic type has an earlier onset, has no jaundice-free interval, and is associated with other non-hepatic anomalies or syndromic features, such as isolated cardiovascular and gastrointestinal anomalies (intestinal malrotation, preduodenal portal vein, abdominal situs inversus) and splenic anomalies (polysplenia, asplenia). The acquired type is not associated with other congenital anomalies, usually occurs in an otherwise healthy term infant, and has a jaundice-free interval followed by the development of jaundice in the first few postnatal weeks. Both forms share the cardinal features of cholestatic jaundice, hepatomegaly, and acholic stools.

EHBA was universally fatal before the Kasai hepato-
portoenterostomy was introduced by Dr Morio Kasai in 1959. This procedure establishes bile flow in up to 80% of patients if performed prior to 60 days after birth. The success rate decreases as the infant’s age increases, with bile flow established in up to 45% of infants 60 to 90 days of age and 10% of infants 90 to 120 days of age. These results underscore the importance of diagnosing this condition early. Approximately one third of patients require liver transplant in the first postnatal year, one third require it in their teens, and one third live with some liver function after the Kasai procedure into adulthood. It is estimated that approximately 50% of patients who have good results from the initial Kasai surgery still become transplant candidates later in life.

“Idiopathic” Neonatal Hepatitis

“Idiopathic” neonatal hepatitis, also known as “giant cell” hepatitis, used to be considered the most common cause of neonatal cholestasis. However, its relative occurrence has decreased as specific disorders that cause a similar clinical and histologic picture have been identified (eg, alpha-1-antitrypsin deficiency, defective bile acid synthesis and transport). The diagnosis is made in infants who have prolonged cholestatic jaundice and typical biopsy findings of disrupted hepatic architecture, multinucleated “giant” hepatocytes, focal hepatocyte necrosis, expansion of portal triads with inflammatory infiltrate, and extramedullary hemapoiesis in addition to the absence of another disorder. Electron microscopy often is useful in diagnosis.

The prognosis of “idiopathic” hepatitis is variable and depends on whether a metabolic or infectious cause ultimately is diagnosed. Jaundice usually resolves by 3 to 4 months of age; persistence of jaundice beyond this age warrants additional evaluation.

Alagille Syndrome (AGS)

AGS also is known as syndromic bile duct paucity or arteriohepatic dysplasia. It is an autosomally dominant inherited with low penetrance disorder of bile duct paucity that occurs in conjunction with syndromic extrahepatic findings. The defect in AGS is a mutation of the Jagged 1 (JAG1) gene, which is mapped to chromosome 20p12 and encodes a ligand for the Notch signaling pathway, which is important in cell fate determination. The diagnosis can be made in the patient who has a marked reduction of intrahepatic bile ducts on liver biopsy in association with other cardiac, ocular, skeletal, and facial abnormalities. The bile duct paucity may not be apparent in early infancy. AGS usually presents in the first 3 postnatal months and must be distinguished from biliary atresia and other causes of nonsyndromic paucity. It may be diagnosed in older children who have persistent cholestatic jaundice and in adults after diagnosis in a related child.

In the original series described by Alagille in 1975, 15 of 30 patients who had cholestatic jaundice and hepatic ductular hypoplasia with intact extrahepatic bile
ducts had other common features. These included a characteristic facies (prominent forehead, deep-set eyes with mild hypertelorism, straight nose, and small, pointed chin), a systolic murmur caused by peripheral pulmonic stenosis, vertebral arch defects, growth retardation, mild-to-moderate mental retardation, and hypogonadism in boys. Emerick and associates (3) studied 92 patients who had AGS and found cholestasis in 96%, bile duct paucity in 85%, cardiac murmur in 97%, vertebral anomalies in 51%, characteristic facies in 96%, eye findings (posterior embryotoxon) in 78%, and renal anomalies in 40%. Minor features included growth retardation (87%), mental retardation (2%), developmental delay (16%), and pancreatic insufficiency (41%). Alagille and colleagues (4) have recommended that the diagnosis be made by confirming the existence of cholestasis and two of the other four abnormalities.

Factors that contribute significantly to mortality in AGS include cardiac disease (other cardiac defects besides peripheral pulmonic stenosis such as tetralogy of Fallot), intracranial hemorrhage, and progressive liver disease.

### Alpha-1-Antitrypsin Deficiency

Alpha-1-antitrypsin is a member of the serine protease inhibitor family (the serpins) that protects the connective tissue from degradation by inhibition of neutrophil elastase, cathepsin G, and proteinase 3. Although lung disease associated with alpha-1-antitrypsin deficiency is attributed to markedly reduced concentrations, liver disease results from retention of the abnormally folded protein in the endoplasmic reticulum (ER) of the hepatocyte (the site of synthesis of most alpha-

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**Table 1. Differential Diagnosis of Cholestatic Jaundice in the Infant**

<table>
<thead>
<tr>
<th>Obstructive</th>
<th>Hepatocellular</th>
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<tbody>
<tr>
<td>● Extrahepatic biliary atresia</td>
<td>● Idiopathic neonatal hepatitis</td>
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<tr>
<td>● Choledochal cyst</td>
<td>● Disorders of the intrahepatic bile ducts</td>
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<tr>
<td>● Spontaneous perforation of the bile duct</td>
<td>– Alagille syndrome (arteriohepatic dysplasia/syndromic paucity of the intrahepatic bile ducts)</td>
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<tr>
<td>● Inspissated bile</td>
<td>– Nonsyndromic paucity of the intrahepatic bile ducts</td>
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<td>● Mass: stone, tumor</td>
<td>– Congenital hepatic fibrosis with bile duct cysts (Caroli disease)</td>
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<td>● Metabolic disorders</td>
<td>● Disorders of amino acid metabolism</td>
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<td></td>
<td>– Tyrosinemia</td>
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<td>– Disorders of lipid metabolism</td>
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<td>– Gaucher disease</td>
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<td>– Niemann–Pick disease</td>
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<td>– Cholesterol ester storage disease (Wolman syndrome)</td>
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<td>– Disorders of carbohydrate metabolism</td>
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<td>– Galactosemia</td>
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<td>– Hereditary fructose intolerance</td>
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<td>– Glycogen storage disease</td>
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<td>– Disorders of bile acid metabolism and transport excretion</td>
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<td></td>
<td>– Zellweger syndrome and other disorders of peroxisomal metabolism</td>
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<td></td>
<td>– Disorders of bilirubin transport (do not cause cholestatic liver injury)</td>
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<td></td>
<td>– Dubin–Johnson syndrome</td>
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<td>– Rotor syndrome</td>
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<td>– Mitochondrial disorders</td>
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<td>– Alpha–1-antitrypsin deficiency</td>
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<td>– Cystic fibrosis</td>
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<td>– Neonatal iron storage disease</td>
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<td>● Endocrine disorders</td>
<td>● Disorders of bile acid metabolism and transport excretion</td>
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<td></td>
<td>– Hypothyroidism</td>
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<td>– Hypopituitarism and septo-optic dysplaesa</td>
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<tr>
<td>● Infectious</td>
<td>● Disorders of bile acid metabolism and transport excretion</td>
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<td></td>
<td>– Sepsis (urinary tract infection, endotoxemia, enterocolitis)</td>
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<td></td>
<td>– TORCH infections (toxoplasmosis, cytomegalovirus, herpesvirus, rubella, syphilis)</td>
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<td>– Hepatitis B, non-typeable hepatitis</td>
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<td>– Human immunodeficiency virus</td>
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<td>● Drugs and Toxins</td>
<td>● Other</td>
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<td>– Total parenteral nutrition</td>
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<td>– Medications</td>
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<td>– Fetal alcohol syndrome</td>
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<td>● Other</td>
<td>– Vascular anomalies</td>
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<td>– Budd–Chiari syndrome</td>
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<td>– Hepatoendothelioma/hemangioma</td>
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<td>– Cardiac insufficiency and hypoperfusion</td>
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<td>– Chromosomal abnormalities</td>
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<td>– Trisomy 21</td>
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<td>– Trisomy 18</td>
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Alpha-1-antitrypsin deficiency is the most common genetic cause of acute and chronic liver disease in children.

Jaundice in the Older Child/Adolescent

New-onset cholestatic jaundice in the older child and adolescent always requires additional investigation. It is essential to fractionate the bilirubin to differentiate cholestatic jaundice from unconjugated hyperbilirubinemia due to hemolysis or defective bilirubin conjugation, as occurs in Gilbert syndrome.

**Wilson Disease**

Wilson disease is an autosomal recessive disorder of copper homeostasis. The affected gene is on chromosome 13 and encodes a highly conserved copper-transporting P-type adenosine triphosphatase (ATP7b) that excretes copper into bile. Copper is an essential trace element that participates in cellular respiration, iron oxidation, pigment formation, and antioxidant defense. It is absorbed from copper-rich foods from the stomach and duodenum, bound to ceruloplasmin in the circulation, and excreted by the liver into bile.

The prevalence of Wilson disease is 1 in 30,000 and is equal among all ethnic groups. The condition presents in most patients as either hepatic or central nervous system involvement. Liver disease occurs at an average age of 10 to 13 years in 45% of patients and rarely is seen before 3 years of age. Some 35% of patients present with neurologic signs (tremor, rigidity, dysarthria) a decade older than patients who have hepatic involvement; 10% present with psychiatric disturbances (depression, new-onset school problems, impulsive behavior); and 10% present with other manifestations, including hemolytic anemia, Fanconi syndrome (glycosuria, aminoaciduria), and cardiomyopathy. Thus, patients who have Wilson disease can have a mixed conjugated and unconjugated hyperbilirubinemia, depending on which disease manifestations are present.
Hepatic involvement ranges from asymptomatic transaminitis to acute liver failure with jaundice, cirrhosis, hepatic necrosis, and encephalopathy. Liver biopsy can show nonspecific findings of steatosis and glycogen deposition. Micronodular cirrhosis and piecemeal necrosis also can be seen. Kaiser-Fleischer (KF) rings, representing copper deposition in Descemet’s membrane, are visible on a slitlamp examination of the eye. Neurologic symptoms are attributed to copper deposition in the basal ganglia and include parkinsonian symptoms. KF rings often are present in patients who have neurologic symptoms, but may be absent in patients who have liver disease.

Wilson disease is diagnosed in the patient who has signs and symptoms consistent with the disease in addition to laboratory findings of impaired hepatic copper metabolism. The serum ceruloplasmin concentration is decreased because copper is not conjugated to the apoceruloplasmin synthesized by the hepatocyte. The unconjugated apoceruloplasmin is degraded rapidly. Measurement of urinary copper in a 24-hour collection is increased. A liver biopsy quantitating hepatic copper content is a helpful diagnostic tool, and a liver that has normal copper content excludes the diagnosis. A slitlamp examination can be performed to evaluate for KF rings. Definitive genetic testing is now available for Wilson disease.

Therapy is geared toward attaining and maintaining normal copper homeostasis. Oral D-penicillamine and trientine are copper chelators. Zinc acetate prevents the absorption of copper from the gastrointestinal tract. Patients are counseled to avoid copper-rich foods such as shellfish, legumes, nuts, chocolate, and liver. Liver transplantation is the treatment of choice for selected patients who have either advanced liver disease or fulminant liver failure.

Autoimmune Hepatitis (AIH)
AIH is an inflammatory hepatitis characterized by the development of pathologic autoantibodies to normal host proteins and a dense mononuclear infiltrate in the portal tracts in the absence of another cause. AIH can be subdivided into two general categories classified by the type of autoantibodies produced: anti-nuclear antibody/anti-smooth muscle antibody (ANA/SMA) AIH, and anti-liver kidney microsomal antibody 1 (LKM1) AIH.

In a study of 52 patients who had AIH, investigators found that the median age at presentation of ANA/SMA AIH was 10.5 years and that for LKM1 AIH was 7.4 years. (7) Some 75% of patients were female. Three patterns of presentation were noted:

1) Acute hepatitis was the pattern in most patients having both types, with nausea, vomiting, anorexia, fatigue, and abdominal pain, followed by jaundice, dark urine, and pale stools. Duration of illness varied from 2 weeks to 2 months in this group.

2) Another group (30%) had the insidious onset of disease of longer duration (6 mo to 2 yr), with relapsing jaundice, progressive fatigue, headache, anorexia, and weight loss.
3) A small percent of patients, who had no prior history of jaundice, had complications of portal hypertension.

AIH is suspected on the basis of clinical characteristics and demonstration of the autoantibodies, as well as an elevated immunoglobulin G value. Definitive diagnosis is made on liver biopsy, where the typical histologic picture is a dense mononuclear infiltrate invading the hepatic parenchyma (periportal hepatitis), with periportal necrosis. In most cases, the disease responds well to immunosuppressive therapy. Urgent liver transplantation is indicated if the patient presents in acute fulminant hepatic failure.

Evaluation of the Jaundiced Patient

Although jaundice is relatively common in the first 2 weeks after birth and is observed frequently in newborns, jaundice in the older infant and child always is abnormal and requires more investigation. Additional evaluation of children who have conjugated hyperbilirubinemia and chronic liver disease should involve looking for the complications of cholestasis, such as coagulopathy, fat malabsorption, ascites, and encephalopathy, to initiate appropriate therapy. Finally, a child who has conjugated hyperbilirubinemia or evidence of chronic liver disease should be referred to a pediatric gastroenterologist.

**The key laboratory test to obtain when evaluating jaundice is fractionation of the bilirubin.**

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History

The age of the patient and history of presentation give important clues to the cause of the jaundice. Some conditions of infantile cholestasis and conjugated hyperbilirubinemia present early in life, such as biliary atresia, AGS, and inherited metabolic disorders. Others often manifest beyond infancy, such as AIH and Wilson disease. Diseases such as cystic fibrosis and alpha-1-antitrypsin deficiency can present as either neonatal cholestasis or later in life as chronic liver disease.

Signs such as poor feeding, irritability, and vomiting may be associated with a metabolic condition, such as galactosemia, or suggest encephalopathy. The presence of acholic stools suggests an obstructive process such as biliary atresia, choledochal cyst, or gallstone disease. Additionally, the birth and perinatal histories, past medical and surgical histories, family history (including consanguinity), medication and dietary histories, social activity and school performance histories, and travel history should be sought.

**Physical Examination**

The clinician should note if the patient is well- or ill-appearing as well as irritable or drowsy. Both signs may indicate encephalopathy, infection, or metabolic derangement. Microcephaly in the infant may indicate congenital infection. Recognition of dysmorphism is valuable. Eyes should be examined for posterior embryotoxon or KF rings. The systolic murmur of peripheral pulmonic stenosis, usually heard in the back as well as the front, suggests AGS. Hepatomegaly typically is present, but a small liver may indicate cirrhosis and end-stage liver disease. Splenomegaly, ascites, and prominent vasculature such as caput medusa suggest portal hypertension and chronic liver disease. An infant’s diaper should be examined for pale stools and dark urine. Neurologic evaluation should be undertaken for ataxia and asterixis.

**Laboratory Tests**

The key laboratory test to obtain when evaluating jaundice is fractionation of the bilirubin. Indirect or unconjugated hyperbilirubinemia usually indicates excessive red blood cell destruction at any age. Direct or conjugated hyperbilirubinemia indicates a hepatobiliary disorder. Hepatic transaminase concentrations are elevated in the presence of hepatocellular injury. The alkaline phosphatase and gamma glutamyl transferase values often are increased with obstructive conditions. Liver function, including prothrombin time, albumin, and cholesterol, should be measured. The remainder of the evaluation should be tailored to the specific patient. Hemolytic anemia can be seen in patients who have Wilson disease. Thyroid function tests can be obtained if hypothyroidism is suspected. Other age-specific tests may be considered, including TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex) titers, blood and urine cultures, alpha-1-antitrypsin Pi phenotype, iron profile, chloride sweat test, urine-reducing substances (galactosemia), and a metabolic screen in young infants. Testing for Wilson disease (ceruloplasmin) or for AIH is appropriate in older children.
Imaging
Real-time ultrasonography is an important diagnostic tool in the evaluation of the jaundiced patient. The absence of a gallbladder on a fasting examination in an infant is suggestive but not diagnostic of biliary atresia. Ultrasonography may demonstrate gallstones, choledochal cyst, or ascites. A Doppler ultrasonographic study of the portal circulation may identify portal hypertension or portal vein thrombosis. Hepatobiliary scintigraphy with technetium-labeled iminodiacetic acid analogs may help differentiate obstructive jaundice from nonobstructive causes. In the case of obstructive jaundice, the hepatic uptake of tracer is normal, but there is no intestinal excretion. In cases of severe hepatocellular disease, uptake into the liver is delayed, but tracer eventually is excreted into the intestine. Premedication with phenobarbital for 3 to 5 days prior to the study enhances biliary excretion and imaging of the isotope.

Liver Biopsy
Ultimately, many patients require a liver biopsy for definitive and reliable diagnosis. The liver biopsy can be performed percutaneously, with or without ultrasonographic guidance, or surgically. In addition to evaluation by an experienced pathologist for specific histologic features, liver tissue can be used to quantify iron and copper content and for electron microscopy to detect certain metabolic conditions.

Management of Jaundice
Treatment is directed at the specific underlying disorder, although persistent cholestasis generally can cause retention of bile acids, bilirubin, and cholesterol; decreased excretion of bile acids into the intestine with resulting fat malabsorption; and hepatocellular damage that eventually causes portal hypertension and end-stage liver disease. Some general principles apply to the management of these consequences independent of the specific cause. These principles include optimizing nutrition by employing the use of medium-chain triglyceride-containing formula or supplements and monitoring fat-soluble vitamin concentrations with supplementation. Management of the complications of chronic liver disease and portal hypertension in conjunction with a pediatric gastroenterologist is essential. All children, particularly those who have chronic liver disease, should be immunized, including both hepatitis A and B, using the guidelines of the American Academy of Pediatrics. It is appropriate to refer any child who evidences acute, severe liver disease or a chronic liver condition to a pediatric transplant center for evaluation.

References

Suggested Reading
PIR Quiz
Quiz also available online at www.pedsinreview.org.

1. Conjugated hyperbilirubinemia is:
   A. A marker of accelerated hemoglobin breakdown.
   B. A normal finding in otherwise healthy adolescents.
   C. Always linked with cholestasis.
   D. Less common than unconjugated hyperbilirubinemia.
   E. Synonymous with direct hyperbilirubinemia.

2. A 4-week-old breastfeeding boy is jaundiced and has a total bilirubin concentration of 13 mg/dL (222.3 mmol/L). The laboratory test that maximizes diagnostic efficiency is:
   A. A complete blood count.
   B. A reticulocyte count.
   C. Bilirubin fractionation.
   D. Gamma glutamyl transferase.
   E. Hepatic transaminase.

3. A 4-week-old breastfeeding boy has become increasingly jaundiced. The pregnancy was unremarkable. Delivery was at term, and the infant was appropriate for gestational age. The jaundice was not noted in the hospital. Findings on the physical examination, other than jaundice, are unremarkable. Today, the total bilirubin concentration is 13 mg/dL (222.3 mmol/L), with a direct fraction of 6 mg/dL (102.6 mmol/L). Of the following, the condition that is most likely ruled out by these findings is:
   A. Alagille syndrome.
   B. Alpha-1-antitrypsin deficiency.
   C. Extrahepatic biliary atresia.
   D. Neonatal hepatitis.
   E. Physiologic jaundice.

4. A previously healthy 15-year-old girl develops jaundice and fatigue. She does not complain of colicky abdominal pain associated with meals. She has had no known exposure to hepatotoxins. Aside from jaundice and appearing mildly ill, findings on her physical examination are unremarkable. Initial laboratory evaluation reveals a bilirubin concentration of 11 mg/dL (188.1 mmol/L) with a direct fraction of 4 mg/dL (68.4 mmol/L), and elevated hepatic transaminases, but no evidence of Epstein-Barr or hepatitis A, B, or C virus. As suspected from the history, ultrasonography reveals a normal gallbladder and biliary tree. Serum ceruloplasmin and autoantibody results are inconclusive. Pi typing reveals PiMM, and the patient proceeds to liver biopsy. Copper content of the sample is normal. Of the following, the patient is most likely to have:
   A. Alpha-1-antitrypsin deficiency.
   B. Autoimmune hepatitis.
   C. Choledochal cyst.
   D. Gilbert syndrome.
   E. Wilson disease.

5. Wilson disease is diagnosed definitively through:
   A. Genetic testing.
   B. Liver biopsy.
   C. Serum ceruloplasmin concentrations.
   D. Slitlamp examination.
   E. Urinary copper excretion.
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