Differential Diagnosis in Pediatrics

R Arvind

JAYPEE

Contents

SECTION 1

SECTION 2

SECTION 3

SECTION 4

SECTION 5

SECTION 6

SECTION 7

SECTION 8

SECTION 9

SECTION 10

SECTION 11

SECTION 12

SECTION 13

SECTION 14

SECTION 15

SECTION 16

SECTION 17

SECTION 18

SECTION 19

SECTION 20

SECTION 21

SECTION 22

CHAPTER 236

Jaundice

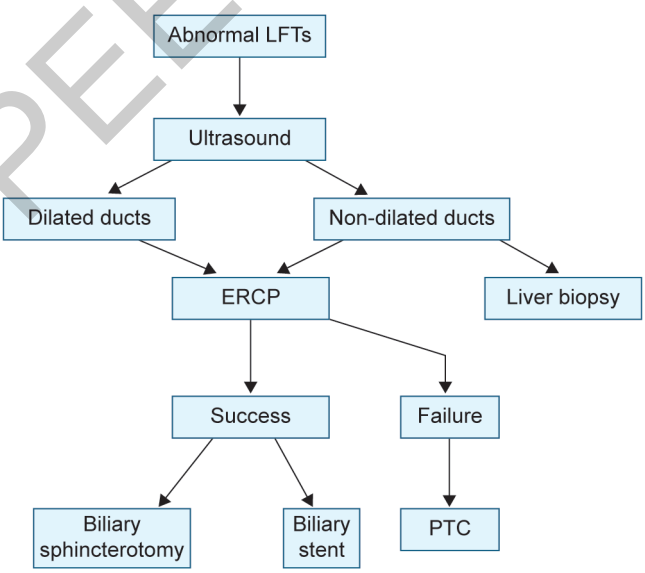
Jaundice may be caused by a raised conjugated or unconjugated bilirubin. Unconjugated hyperbilirubinemia may be due to excessive production of bilirubin (hemolysis), reduced uptake of bilirubin, or a failure of conjugation by the liver. Conjugated hyperbilirubinemia results from hepatocellular damage or obstruction of the bile ducts, either within the liver (intrahepatic cholestasis) or of a major bile duct (extrahepatic obstruction jaundice). Jaundice is also often classified into pre-hepatic (hemolysis), hepatic, and extrahepatic types.

HISTORY

Chronic fatigue, though nonspecific, is a common symptom of liver disease and should trigger at least a basic evaluation including aminotransferases even in the absence of overt jaundice **(Flowchart 1)**. Myalgias, nausea, vomiting, and fever are often seen in patients with viral hepatitis or autoimmune hepatitis.

Acute biliary obstruction is signaled by right upper quadrant pain, vomiting, fever, and acholic stools in addition to jaundice.

Flowchart 1: Evaluation of cholestatic jaundice.



(ERCP: endoscopic retrograde cholangiopancreatography; LFTs: liver function tests; PTC: percutaneous transhepatic cholangiography)

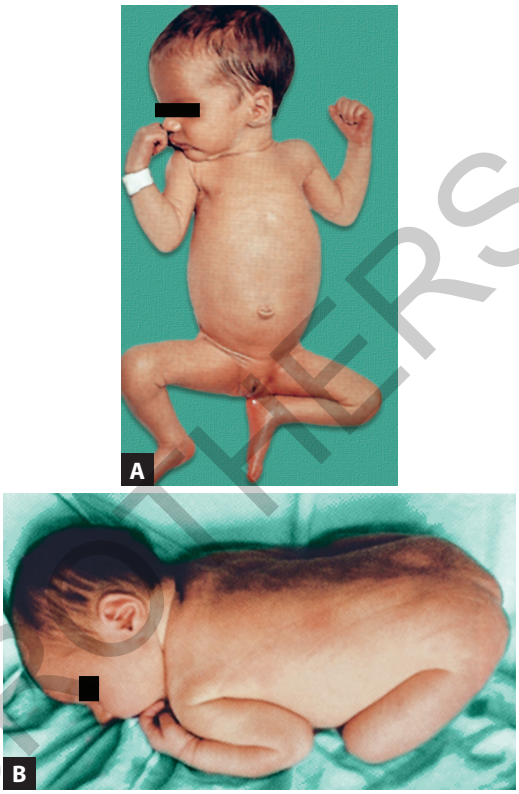
Neurologic and psychiatric symptoms may be among the manifestations of Wilson disease. Autoimmune hepatitis may be accompanied by manifestations of other autoimmune disorders.

The child's age at the onset of symptoms may be helpful. Wilson disease commonly manifests in school-aged children and adolescents. Similarly, autoimmune hepatitis is most prevalent in school-aged children and adolescents with female predominance. A thorough history should include past and present use of prescription, over-the-counter (e.g., acetaminophen), and street drugs.

Symptoms of cholestasis such as jaundice, dark urine, steatorrhea, symptoms of fat-soluble vitamin deficiency, failure to thrive, and pruritus should be explored in detail.

CLINICAL FEATURES

The clinician should focus on signs of portal hypertension—spider angiomas, palmar erythema, dilated abdominal veins, ascites, and splenomegaly with a small liver **(Figs. 1A and B)**. Cutaneous excoriation as evidence of pruritus, xanthomas, and jaundice support cholestasis. Clubbing of digits may suggest hepatopulmonary syndrome. A large, tender liver is suggestive of acute viral hepatitis or congestive heart failure. A small liver may be found in patients with severe hepatitis or cirrhosis. A tender gallbladder is indicative of choledocholithiasis or cholecystitis. Abnormal neurologic findings, including tremor, fine motor incoordination, clumsy gait, and choreiform movements, suggest Wilson disease. A slit-lamp examination should be included to look for the Kayser–Fleischer rings (a brownish discoloration at the periphery of the cornea) of Wilson disease.



Figs. 1A and B: Jaundice.

CAUSES

- *Hemolytic (pre-hepatic):*
  - Red blood cell (RBC) membrane defects
    - Spherocytosis
    - Elliptocytosis
  - RBC enzyme defects
    - Glucose-6-phosphate dehydrogenase (G6PD) deficiency
  - Globin chain synthesis defect—thalassemic
  - Acquired hemolysis
    - Drug—surfs
    - Penicillin
    - Anti malaria
- *Liver cell disease:*
  - Neonatal jaundice

- Viral hepatitis
- Crigler–Najjar syndrome
- Gilbert's disease
- Galactosemia
- Hypothyroidism
- Intrauterine infection

- *Obstructive (posthepatic):*
  - Biliary atresia
  - Choledochal cyst
  - Instigated bile
  - Stricture and calculus in biliary tree
  - Alpha-1 antitrypsin deficiency
  - Dubin–Johnson syndrome
  - Rotor syndrome

UNCONJUGATED HYPERBILIRUBINEMIA

A complete blood count with evaluation of the smear, reticulocyte count, and Coombs test can differentiate hemolytic from nonhemolytic disorders.

Erythrocyte membrane defects (spherocytosis) and enzyme defects (pyruvate kinase deficiency, G6PD) may not be apparent until childhood or adolescence. Acquired autoimmune hemolytic anemia is characterized by pallor, abdominal pain, fever, and dark urine in addition to jaundice. Laboratory studies document anemia and reticulocytosis. The direct Coombs test result is positive. Hemolytic anemia can be associated with infection, immunodeficiency, malignancy, hemolytic uremic syndrome, or other autoimmune disorders, such as systemic lupus erythematosus, rheumatoid arthritis, thyroid disorders, and autoimmune hepatitis.

Unconjugated hyperbilirubinemia can be caused by congestive heart failure and infection should in such circumstances extrahepatic symptoms, cardiac failure, or sepsis dominate the picture. If no other explanation is found, Gilbert syndrome or Crigler–Najjar syndrome type II should be considered.

This condition is due to:

- *An increased production of bilirubin:*
  - Inefficient marrow production
  - Increased breakdown (hemolysis)
    - Hemoglobinopathies
    - Antibody-mediated
    - Drug-induced
- Decreased uptake of bilirubin into the liver; Gilbert's disease
- *Decreased conjugation of bilirubin in the liver:*
  - Crigler–Najjar syndrome
  - Neonatal jaundice
  - Drugs
  - Lucey–Driscoll syndrome

Viral Hepatitis

Infection

Infections are a common cause of jaundice in the child and adolescent. The most important step is to evaluate patients for synthetic liver failure and for signs of chronicity (portal hypertension, growth failure, risk factors for blood-borne, or sexually transmitted disorders). Patients with synthetic liver failure should be referred for urgent evaluation by the liver transplant center.

Hepatitis A virus (HAV) infection is usually anicteric or asymptomatic in children <5 years of age. About 2–7 days before the onset of jaundice, there is a flulike illness with symptoms that can include malaise, headache, myalgias, anorexia, vomiting, diarrhea, right upper quadrant pain, and fever. Some children present with cough and coryza. The urine becomes dark, and jaundice and pale or acholic stools develop. Aminotransferase levels are 10–100 times normal. The diagnosis is confirmed by an HAV IgM study. Children generally recover within 2 weeks.

Acute hepatitis C virus (HCV) infection is often mild and usually subclinical. Jaundice

is unusual. Screening for hepatitis uses anti-HCV antibodies, and infection is confirmed via polymerase chain reaction (PCR) for HCV RNA. Transmission may be parenteral due to IV drug use or exposure to blood, or sexual or vertical transmission is also possible.

Wilson's Disease

Wilson disease is an autosomal recessive disorder of copper metabolism. As a result of ATP7B mutation, copper cannot be excreted and it accumulates in the liver, which causes hepatic steatosis and necrosis. Copper is then released into the circulation and is ultimately deposited in the central nervous system, kidneys, and cornea. The hepatic manifestation predominates in childhood; a neuropsychiatric manifestation becomes more common later, in adolescence and adulthood. The liver involvement may manifest as acute hepatitis, fulminant hepatic failure, chronic hepatitis, cirrhosis, or asymptomatic elevation of serum aminotransferases. Neurologic symptoms such as dysarthria, clumsiness, tremor, and mood disorders may or may not be present. In the kidney, the result is tubular dysfunction; in the cornea, the result is Kayser–Fleischer rings. Hemolysis can be present as a result of copper toxicity. The diagnosis is supported by documenting a low serum ceruloplasmin level, high urinary copper excretion, and increased hepatic copper concentrations on liver biopsy.

Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is a common cause of chronic liver injury. The most frequent course is insidious with fatigue as a dominant symptom. Autoimmune hepatitis can present acutely with malaise, anorexia, nausea, vomiting, and jaundice. Autoimmune disorders such as arthritis, thyroiditis, vasculitis, nephritis, hemolytic anemia, or diabetes mellitus are often associated with AIH.

Biliary Disease

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is characterized by focal dilatation and stenosis of the intrahepatic or extrahepatic bile ducts with surrounding fibrosis resulting from an inflammatory process. It can manifest from early childhood through adulthood.

Extrahepatic Biliary Obstruction

Gallstones

Gallstones are particularly common in children with hemolytic disorders, such as sickle cell disease, thalassemia, erythrocyte membrane defects, erythrocyte enzyme defects, and autoimmune hemolytic anemia. The mean age at presentation is 12 years. Gallstones are also associated with anatomic abnormalities of the biliary tract, cystic fibrosis, ileal dysfunction, obesity, parenteral nutrition, sepsis, prematurity, and pregnancy.

JAUNDICE IN THE NEONATE AND INFANT

Physiologic and Breast Milk Jaundice

In neonates, increased bilirubin production is caused by the normally increased neonatal red blood cell mass and the decreased life span of the red blood cells (80 vs. 120 days). Albumin binding is decreased because of lower albumin concentrations and diminished binding capacity, which results in decreased transport of unconjugated bilirubin (UCB) to the liver with increased deposition in tissues. Uptake of bilirubin by the hepatocytes during the 1st weeks of life is defective. Low levels of glutathione S-transferase B decrease intracellular binding,

which may impede the transport of UCB to the endoplasmic reticulum. Conjugation is impaired by decreased activity of uridine diphosphate glucuronosyltransferase (UDPGT). Secretion into the canaliculi is impaired. There is increased enterohepatic circulation of unconjugated bilirubin as a result of increased concentrations of β-glucuronidase in the intestinal lumen and as a result of decreased intestinal bacterial flora, leading to diminished urobilinogen formation.

These features contribute in varying degrees to physiologic jaundice, characterized by a peak bilirubin level of <13 mg/dL on postnatal days 3–5, a decrease to normal by 2 weeks of age, and a conjugated fraction of <20%. In premature, breastfed infants of diabetic mother, the peak is higher and lasts longer. Conjugated bilirubin should be checked if there is any question of the nature of jaundice.

Breastfeeding has been associated with an increased incidence of unconjugated hyperbilirubinemia outside the expected range (>13 mg/dL). Jaundice of this level may occur in 10–25% of breastfed infants, in contrast to 4–7% of formula-fed infants. It can occur within the 1st 5 days of life and is referred to as "early" or "breastfeeding" jaundice. Breastfeeding jaundice is seen in infants who are not feeding adequately and may be dehydrated or malnourished. In a second group of breastfed infants, the jaundice develops slowly, occurring after the first week of life, and peaks between the 2nd and 3rd weeks of life at 10–20 mg/dL. This is referred to as "late" or "breast milk" jaundice. The precise cause of increased bilirubin levels in this latter setting has not been established; alternative theories include inhibition of glucuronosyltransferase activity and increased enterohepatic circulation of UCB. Kernicterus appears to be very rare but has been reported in association with breastfeeding. No treatment is necessary for physiologic jaundice **(Fig. 2)**.

Polycythemia: Neonatal polycythemia, defined as a hematocrit >65% by venipuncture, can be caused by maternal diabetes, maternal-fetal, or twin-twin transfusion, intrauterine hypoxemia, endocrine disorders, and delayed cord clamping. Polycythemia results in increased bilirubin production because of the increased red blood cell mass.

Hemolytic disorders: Reticulocytosis, unconjugated hyperbilirubinemia, and an increased nucleated red blood cell count, with either a low or normal hematocrit, suggest hemolysis. This can result from isoimmunization; erythrocyte membrane, hemoglobin, or enzyme defects; or sepsis with disseminated intravascular coagulation.

Isoimmune hemolytic disease: In this group of disorders, maternal antibodies

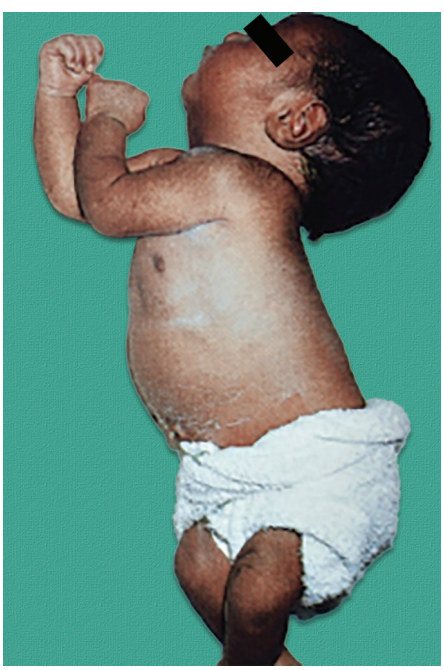


Fig. 2: Kernicterus.

(immunoglobulin G) to the infant's erythrocytes cross the placenta, resulting in red blood cell destruction. The administration of anti-D gamma globulin [RhO(D) immune globulin (RhoGAM)] after delivery to women who are Rh-negative has reduced the incidence of Rh sensitization and erythroblastosis fetalis.

The diagnosis is confirmed by demonstrating that the infant is Rh-positive, that the direct Coombs test result is positive, and that maternal antibody is coating the infant's red blood cells.

ABO blood type incompatibility causes a less severe form of isoimmune hemolytic disease with a less rapid development of jaundice. It is more common in infants with blood type A or B who are born to mothers with blood type O.

Erythrocyte enzyme defects: G6PD deficiency is common. Jaundice is seen more frequently in persons with a Mediterranean or Far Eastern ancestry who have a complete absence of the enzyme. In these individuals, hemolysis can occur without a precipitant. In African-American patients, the disease is generally less severe, and hemolysis is rare without exposure to a drug, toxin, or infection that causes an oxidant stress. G6PD deficiency can manifest as neonatal jaundice on day 2 or 3 after birth; alternatively, it may not manifest until later in childhood, when jaundice is associated with an acute hemolytic crisis. The diagnosis of G6PD deficiency is confirmed by documenting deficiency of the enzyme in red blood cells.

Familial Disorders of Bilirubin Metabolism

Gilbert syndrome is a heterogeneous group of disorders that have in common at least a 50% decrease in UDPGT activity as a result of a defect in the gene responsible for this enzyme. In 20–30% of individuals with Gilbert syndrome, there is also a decrease in hepatocyte bilirubin uptake. Affected individuals are generally asymptomatic and may not present with jaundice until the 2nd or 3rd decade of life. Gilbert syndrome may be responsible for some cases of neonatal jaundice. Mild jaundice with a bilirubin level up to 7 mg/dL can occur transiently with fatigue, exercise, fasting, febrile illness, and alcohol ingestion in older patients.

Crigler–Najjar syndrome: Crigler–Najjar syndrome types I and II (also known as Arias syndrome) are rare autosomal recessive conditions caused by mutations (different alleles from those of Gilbert syndrome) in the gene coding for UDPGT.

The onset of Crigler–Najjar syndrome type II is usually at birth, although it can be in late childhood. There is <5% of the normal UDPGT activity. Bile contains bilirubin monoglucuronides. Bilirubin levels, generally 8–25 mg/dL, respond to phenobarbital administration with a significant decrease. Neurologic disease is rare.

Lucey–Driscoll syndrome: Lucey–Driscoll syndrome is a transient familial neonatal hyperbilirubinemia that appears in the 1st few days of life and resolves by 2–3 weeks of age. This results from the inhibition of UDPGT by a substance that has been found in both maternal and infant serum.

Neonatal Conjugated Hyperbilirubinemia

Common to all of these conditions is the potential for hypoprothrombinemia. If the PT is prolonged, the infant should be treated with intravenous vitamin K to avoid spontaneous hemorrhage, particularly intracranial. Depending on the degree of

hepatocellular damage, vitamin K may not correct the PT.

Hypoglycemia is another danger that is associated with diseases that cause severe hepatic dysfunction, metabolic disorders as well as with hypopituitarism. The infant may be relatively asymptomatic despite significant hypoglycemia. The serum glucose level can be measured before a feeding. If hypoglycemia is present, the infant should receive frequent feedings, continuous feedings, or intravenous dextrose infusions. Glucose level should always be the part of the evaluation of conjugated hyperbilirubinemia.

Obstructive/Anatomic Abnormalities, Idiopathic Cholestasis, and Idiopathic Neonatal Hepatitis

Biliary atresia: Untreated biliary atresia is lethal, and only prompt diagnosis and surgical treatment can prevent mortality. Biliary atresia accounts for approximately 30% of cases of neonatal cholestasis seen at major referral centers. It occurs in one in 8,000–15,000 live births. It is the result of a progressive inflammatory process leading to obliteration of the lumen of the extrahepatic duct. It is the leading indication for liver transplantation in the pediatric population. Infants are less often icteric from birth and more often develop jaundice at 2–6 weeks of age. Infants are usually full term and initially appear healthy except for jaundice, dark urine, and acholic stools. The family history usually is negative for liver disease. There appear to be two forms of biliary atresia:

BOX 1: Conditions not to miss in infants with conjugated hyperbilirubinemia.

- *Priorities:*
  - Hypoprothrombinemia
  - Hypoglycemia
  - Extrahepatic biliary atresia
- *Infections:*
  - Sepsis
  - Urinary tract infection
  - Syphilis
  - Toxoplasmosis
  - Herpes simplex virus
- *Endocrine disorders:*
  - Hypopituitarism
  - Hypothyroidism
- *Metabolic disorders:*
  - Galactosemia
  - Hereditary fructose intolerance (fructosemia)
  - Tyrosinemia
- *Other:*
  - Neonatal hemochromatosis
  - Bile acid abnormalities
  - Choledochal cyst
  - Intestinal obstruction
  - Familial hemophagocytic syndromes
  - Heart disease
  - Toxins

1. In the "embryonic" or "fetal form," which occurs in 15–30% of cases, there is no jaundice-free period. There are often associated defects, including cardiac defects, polysplenia, malrotation, and situs inversus.
2. In the "perinatal form," there may be a jaundice-free interval after resolution of the normal physiologic jaundice, and there are no associated anomalies.

There are a few conditions "Not to Miss in Infants with Conjugated Hyperbilirubinemia" given in **Box 1**.

Differential Diagnosis in Pediatrics

Salient Features

- All the symptoms and signs related to pediatrics have been listed in alphabetical order
- Symptoms and signs have been discussed completely up to the possible clinical diagnosis level. This includes definition, pathophysiology, causes, techniques to elicit, and impression of the respective symptoms and signs
- Clinical approaches, such as general examination, systemic examination, investigations, and relevant procedures, to reach a diagnosis have been discussed
- Wherever possible, these have been illustrated with photographs
- This book acts as a ready reckoner for the reader to search for any symptoms and signs in an indexing format and go through them completely in a single place
- The reader need not go to different pages or books for material, as all the possible information have been compiled at one place
- This is useful to undergraduates and postgraduates for reading text as well as preparing for competitive examinations
- This is useful to academic pediatricians and practicing pediatricians to brush up their clinical skill as well as clinical knowledge to help themselves reach a clinical diagnosis
- This is a clinical pediatric book presented in a unique way.

R Arvind MBBS DCH DNB is one of the well-known Pediatricians in Bengaluru, Karnataka, India. He is Consultant Pediatrician and Neonatologist. He is Proprietor and Medical Director of Vathsalya Speciality Clinic, Bengaluru. He received his medical degree from Bangalore Medical College and Research Institute, Bengaluru, in 1988 and postgraduate degree from Bellary Medical College, Bellary, Karnataka, in 1992. He had worked in the Department of Nephrology, St John's Medical College Hospital, Bengaluru. He has authored many reference books in pediatrics for medical students, being published by international publishers. Many of his papers and articles have been published in leading international journals and magazines.

Shelving Recommendation
PEDIATRICS

ISBN 978-93-6616-259-1