Evaluation of jaundice in children beyond the neonatal period

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Abstract

Jaundice is an important sign of acute and chronic liver diseases in children and adolescents. The spectrum of aetiologies is broad and differs from those presenting in neonates. Chronic liver disease may not present with jaundice until late in the disease. In contrast, acute onset jaundice may be a sign of severe liver disease which may progress to fulminant liver failure. Therefore, prompt diagnosis and evaluation of liver synthetic function will identify serious conditions that require referral to specialised units for assessment and consideration of liver transplantation. This review provides a systematic approach to the evaluation of jaundice in children and adolescents and an overview of the differential diagnoses.

Keywords acute; adolescent; autoimmune liver disease; child; cholestasis; drug-induced liver disease; hepatitis; hyperbilirubinemia; jaundice; liver failure

Jaundice, defined as yellow discolouration of skin, sclera and mucous membranes, is a sign of hyperbilirubinemia (total serum bilirubin more than 17 μmol/litre). The degree of jaundice directly relates to the level of serum bilirubin but is rarely visible when below 50 μmol/litre. It may result from excess bilirubin production as in haemolysis, or reduced bilirubin elimination in liver disease.

The aetiology varies according to age. In neonates, jaundice may be physiological, due to haemolysis, secondary to sepsis such as intrauterine infections or urinary tract infections, or to neonatal liver disease, e.g. biliary atresia or inherited liver disease. In older children, jaundice may be caused by viral infections such as viral hepatitis A and B, autoimmune liver disease, drug-induced liver injury, genetic, metabolic and anatomical hepatobiliary anomalies and haematological disease.

It is important to differentiate self-limiting disease from serious liver disease. Acute onset jaundice may be the first symptom of acute hepatitis or fulminant liver failure. Jaundice may be a late manifestation of chronic liver disease with progression to cirrhosis and is unusual in diseases such as Cystic Fibrosis Liver Disease and Non-alcoholic fatty liver disease. Therefore, careful assessment using a structured framework for evaluating children and adolescents with jaundice is necessary to make a prompt diagnosis. This review focuses on evaluating children (beyond the first year of life) and adolescents presenting with jaundice due to liver disease, and provides an overview of common differential diagnoses and principles of management.

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History

In common with most diseases a thorough history is important in reaching a diagnosis. The duration of illness usually indicates acute or chronic liver diseases, while growth failure suggests chronic liver disease. Prodromal symptoms including fever, fatigue, anorexia, nausea and abdominal pain preceding the onset of jaundice may indicate an acute viral hepatitis (e.g. Hepatitis A) and identifying exposure to affected individuals, contaminated food and animals, and recent travel is essential. Dark urine and pale stools suggest biliary obstruction, from either intra or extrahepatic causes.

Autoimmune hepatitis may present with either acute or chronic liver disease and be associated with other autoimmune phenomena or family history. Parental consanguinity and family history should increase the suspicion of genetic conditions such as Progressive Familial Intrahepatic Cholestasis (PFIC – see below), Wilson's disease and alpha-1 antitrypsin deficiency, but absence of a history does not preclude these diagnoses as *de novo* cases are common. Family history of infantile death warrants evaluation for inborn errors of metabolism.

Eliciting exposures to hepatotoxic medications including paracetamol, oral contraceptive pill, antibiotics (especially, amoxicillin with clavulanic acid), and valproate are important. Affected individuals may also exhibit other organ dysfunction including renal impairment and altered mental state.

Examination

Physical examination should include an assessment of growth, development, nutrition status and mental state. Jaundice is observed most easily in the sclera. Abdominal examination may reveal hepatomegaly with or without splenomegaly, ascites and distended abdominal wall veins. Peripheral signs of chronic liver disease include palmar erythema, spider naevi, digital clubbing and xanthomas.

Dysmorphic features may indicate genetic abnormalities such as Alagille syndrome. Pallor, bruising, bleeding from venepuncture sites and petechiae typically indicate coagulopathy.

Confusion or coma may be signs of fulminant liver failure or metabolic disease causing hyperammonaemia or hypoglycaemia. Other indications of liver failure include easy bruising, vomiting, and fever. Hepatic flap (asterixis), increased deep tendon reflexes and positive Babinski sign are indicative of advanced hepatic encephalopathy. Foetor hepaticus, a sweet aroma of the breath, is another sign of encephalopathy but is rare in children. Kaiser–Fleischer rings may be observed in Wilson's disease, using a slit lamp in children over 7 years, but they are not always present.

Laboratory investigations

The requirement for laboratory investigations and imaging should be guided by the clinical suspicion of likely differential diagnoses. Causes of jaundice may be divided into those

resulting in predominantly unconjugated hyperbilirubinaemia (direct bilirubin less than 15% of total bilirubin) or conjugated hyperbilirubinaemia (direct bilirubin more than 20% of total bilirubin). Jaundice due to liver and biliary disease is predominantly a conjugated hyperbilirubinaemia. Biochemical markers of liver injury may be broadly divided into two distinct patterns: cholestatic and hepatocellular liver injury. Raised alkaline phosphatase (ALP), gamma glutamyltransferase (GGT) and conjugated bilirubin is characteristic of cholestatic liver diseases or biliary obstruction. Hepatocellular injury from any cause leads to elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST). However, there is considerable overlap between these patterns. Cholestatic injury inevitably leads to hepatocellular dysfunction due to accumulation of noxious bile within hepatocytes. Likewise, hepatocellular disease eventually results in reduced bile flow.

A step-wise investigative approach to children and adolescents presenting with jaundice is outlined in Figure 1. Specific investigations for differential diagnoses are summarised in Table 1.

Differential diagnoses of jaundice due to liver disease

Viral hepatitis

Many hepatotropic (Hepatitis A, E and rarely Hepatitis B) and non-hepatotropic viruses (HHV-6, Epstein–Barr virus (EBV), Varicella-Zoster virus (VZV), enteroviruses and Parvovirus B19) can cause acute hepatitis. Acute onset jaundice associated with dark urine, elevated transaminases (ALT, AST) and conjugated hyperbilirubinaemia is often be preceded by prodromal symptoms of fatigue, anorexia, nausea, abdominal pain, headaches and myalgia with or without fever. Other clues should be sought including exposure to affected individuals, travel to endemic areas (e.g. Hepatitis A), consumption of contaminated food, zoonotic exposure (e.g. Hepatitis E), associated tonsillitis, lymphadenopathy and splenomegaly (e.g. EBV), rash (e.g. HHV-6, enterovirus, Parvovirus B19), arthritis (e.g. Parvovirus B19), and concurrent bone marrow suppression (e.g. Parvovirus B19). In the UK, although acute Hepatitis B & C are reported, children are usually asymptomatic and not jaundiced. In general, Hepatitis B and C in children are secondary to vertical transmission leading to chronic hepatitis which is asymptomatic during childhood.

Diagnosis of viral hepatitis can be confirmed by positive serological tests (Table 2). In some cases, no causative virus is identified (known as sero-negative hepatitis). Although most infections are self-limiting, progression to fulminant liver failure is possible and close evaluation of liver synthetic function and follow-up are warranted.

Gilbert's syndrome

This common benign autosomal recessive condition leads to recurrent, mild unconjugated hyperbilirubinaemia, affecting 3–7% of the general population. Episodes occur during stress, fasting or dehydration, but have no clinical consequences. Liver function tests are otherwise normal. Genetic mutations are most commonly found in the promoter region of a bilirubin conjugating enzyme gene, *UGT1A1*. This gene is also involved in Crigler–Nijjar syndrome types I and II, which cause severe unconjugated hyperbilirubinaemia in neonates with very low enzyme activity and high risk of kernicterus.

Autoimmune liver diseases

Paediatric autoimmune hepatitis (AIH) and autoimmune sclerosing cholangitis (ASC) are progressive, inflammatory conditions associated with circulating auto-reactive antibodies, which present with an acute hepatitis with jaundice, fatigue or chronic liver disease with malnutrition, cirrhosis and portal hypertension.

There are two subtypes of autoimmune hepatitis: AIH-1 and AIH-2. AIH-1 accounts for approximately two-thirds of cases, often manifests at the time of puberty, and is defined by positive anti-smooth muscle and/or anti-nuclear antibodies. In contrast, AIH-2 typically presents at a younger age, more frequently with acute liver failure, more commonly associated with IgA deficiency, and is characterised by anti-liver-kidney-microsomal antibodies. Both subtypes are more common in females after puberty. Other risk factors including a personal or family history of autoimmune disorders (e.g. inflammatory bowel disease) and HLA-DR3 haplotype. Raised IgG and low levels of complement C4 features of AIH-1 and AIH-2. Presentations are variable: acute presentations are similar to acute viral hepatitis (40%), chronic onset of fatigue, anorexia, weight loss and recurrent jaundice over months to years (25–40%), and complications of portal hypertension including variceal haemorrhage (10%).

Children with autoimmune sclerosing cholangitis may present with fatigue, pruritus, abdominal pain, weight loss and intermittent jaundice. They often also present with an incidental finding of hepatomegaly or biochemical changes of cholestasis. They sometimes have features of AIH-1 with bile duct abnormalities (e.g. ductal wall irregularities, beading, and strictures) demonstrable on ERCP or magnetic resonance cholangiopancreatography. Atypical perinuclear anti-neutrophil cytoplasmic antibodies may also be found. Long-term immunosuppressive therapy with corticosteroids and azathioprine is the mainstay, though with variable efficacy.

Drug-induced liver injury

The liver is an important site of drug metabolism. Drug-induced liver injury (DILI) arises when there is an imbalance between generation of toxic metabolites and rate of detoxification. Although DILI is uncommon in children, it is an important cause of acute liver failure. DILI may be due to excessive ingestion of drugs with predictable, dose-dependent hepatotoxicity (e.g. paracetamol). However, many causative drugs lead to idiosyncratic reactions with variable latency between exposure and symptoms. In children, developmental differences in drug metabolism, genetic polymorphisms of metabolising enzymes, nutritional status, concurrent medications and underlying disorders such as mitochondrial dysfunction may increase the susceptibility to hepatotoxicity. For example, polymorphism in mitochondrial gene, *POLG*, is associated with valproate-induced liver failure. Young people with benign recurrent intrahepatic cholestasis are susceptible to oral contraceptive-induced cholestasis.

Paracetamol hepatotoxicity is most common cause of paediatric DILI in the UK. Other important causes in children include antimicrobials, anticonvulsants, non-steroidal anti-inflammatory medications, oral contraceptive pill and chemotherapeutic agents. There is a wide spectrum of clinical presentation. Some offending agents have distinct clinical patterns (Table 3).