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REVIEW

Clinical practice

Neonatal cholestasis

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Abstract Neonatal cholestasis is a serious condition which requires urgent further investigation. Delayed referral of cholestatic neonates, however, is still a significant problem. Every child presenting with jaundice beyond the age of 2 weeks should be evaluated with a fractionated bilirubin checked. In case of neonatal cholestasis, the first step should be the assessment of coagulation and urgent parenteral vitamin K administration in case of coagulopathy and the exclusion of life-threatening conditions or disorders requiring urgent specific treatment. Any child presenting with acholic stools should be referred to a paediatric hepatology unit in order to confirm or rule out biliary atresia, as prognosis after porto-enterostomy correlates with younger age at the time of surgery. Once these conditions have been excluded, a more individualised approach is used based on anamnestic, clinical and further diagnostic findings. Besides specific medical or surgical therapy for selected diseases, early supportive treatment aiming for optimal growth and development and prevention of complications is of uttermost importance.

Keywords Neonatal cholestasis · Jaundice · Conjugated hyperbilirubinaemia · Extrahepatic biliary atresia

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
INR	International normalised ratio
MCT	Medium chain triglycerides
PT	Prothrombin time
Torches	Toxoplasma, others, rubella, cytomegalovirus, herpes simplex, syphilis

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Introduction

Jaundice is a common finding during the first 2 weeks of life.

In the majority of cases, it is caused by physiologic jaundice and breast milk jaundice characterised by unconjugated hyperbilirubinaemia which resolves spontaneously.

Prolonged neonatal jaundice is jaundice persisting or (re) occurring after the second week of life.

This condition requires urgent investigation to differentiate unconjugated hyperbilirubinaemia from infrequent but always pathological neonatal cholestasis, followed by further elucidation of the underlying cause.

This review focuses on the initial approach, diagnostic investigation and medical management of the cholestatic infant.

Definition and incidence

Neonatal cholestasis results from impaired bile formation by the hepatocyte or from obstruction of bile flow through the intra- or extrahepatic biliary tree [13, 26] leading to the accumulation of biliary substances in the liver, blood and extrahepatic tissues.

This manifests as conjugated hyperbilirubinaemia. A direct or conjugated bilirubin of more than 1 mg/dl is generally considered to be abnormal, if the total serum bilirubin is at or below 5 mg/dl. For total serum bilirubin,

values higher than 5 mg/dl, a direct bilirubin fraction of more than 20% of the total bilirubin, is abnormal. The laboratory method used, however, needs to be taken into account. The most commonly used method, the diazo or van den Bergh method, does not specifically measure conjugated bilirubin but reports direct bilirubin (conjugated forms+δ-bilirubin fraction). Ideally, a specific measurement of conjugated bilirubin, such as with the Ektachem system, should be obtained. With this system, a value of conjugated bilirubin greater than 1.0 mg/dl can be used to define cholestasis, regardless of total bilirubin [1].

The incidence of neonatal cholestasis is approximately 1 in 2,500 live births [25].

The most common cause of neonatal jaundice in the term neonate is biliary atresia which comprises approximately one third of cases [20]. Alpha-1-antitrypsin deficiency is the cause in 5% to 15% [8], whereas other inherited forms of cholestasis occur in 10% to 20% of cases. Inborn errors of metabolism and congenital infections (including the 'TORCHES') cause respectively 20% and 5% of cases.

In the 1970s, more than half of the cholestatic infants were designated as having neonatal hepatitis. This category has significantly decreased (currently 10–15%) due to improved diagnostic methods [2]. Table 1 gives a more detailed overview of the different causes of neonatal cholestasis.

Table 1 Differential diagnosis of neonatal cholestasis

Hepatic bile duct abnormalities	Biliary atresia
	Choledochal cyst
	Cholelithiasis
	Inspissated bile secretion
	Spontaneous perforation of bile duct
	Non-syndromic paucity of bile ducts
	Congenital hepatic fibrosis/Caroli disease
	Neonatal sclerosing cholangitis
Idiopathic neonatal hepatitis	
Infections	Viral (TORCH, HIV, Echovirus, Adenovirus, Coxsackie virus, HBV, Parvovirus B19,….)
	Bacterial (sepsis, urinary tract infection, syphilis)
Endocrine disorders	Hypothyroidism
	Hypopituitarism
Genetic/metabolic	Alagille syndrome
	Cystic fibrosis
	Alpha-1-antitrypsin deficiency
	Progressive familial intrahepatic cholestasis
	Tyrosinaemia
	Galactosaemia
	Fructosaemia
	Inborn errors of bile acid metabolism
	Neonatal hemochromatosis
	Gaucher's disease
	Wolman's disease
	Niemann Pick type C
	Mitochondrial disorders
	Congenital disorders of glycosylation
	Peroxisomal disorders
	Dubin Johnson and Rotor syndrome
Chromosomal disorders	Trisomy 21, 13, 18
	Turner syndrome
Toxic	Parenteral nutrition
	Drugs
Systemic disorders	Shock, heart failure
	Neonatal lupus erythematosus
Miscellaneous	Haemophagocytic lymphohistiocytosis
	Neonatal leukaemia
	Erythroblastosis foetalis

Evaluation of the infant with jaundice

Early detection of neonatal cholestasis is very important for several reasons. It allows the early onset of effective treatment of a specific underlying condition which can be infectious or metabolic. Timely surgical management of extrahepatic biliary obstruction is of uttermost importance. Many reports have confirmed that in biliary atresia, the timing of the Kasai procedure correlates directly with outcome. Children with biliary atresia referred for surgery before 60 days of age do dramatically better than those older than 90 days at the time of operation (reestablishment of bile flow in more than 80% versus less than 20%, respectively) [3, 10, 12, 14, 18, 24]. Even when specific treatment is not available, prompt identification of the cholestatic child is essential to provide early supportive treatment and optimal nutritional care in order to prevent complications such as vitamin K deficiency bleeding.

Up to date, late referral of cholestatic infants, however, remains an important problem occurring in more than half of the patients [4, 11, 15, 20]. A lack of awareness about the seriousness of neonatal cholestasis in primary health care providers might be one of the contributing factors. Many of these jaundiced infants do appear otherwise healthy and thrive appropriately, falsely reassuring health visitors, midwifes, physicians and hence parents. The relative rarity of cholestasis is in sharp contrast with the very common finding of jaundice during the first weeks of life, and therefore, a false diagnosis of physiologic or breast milk jaundice is easily made. Symptoms indicative of cholestasis such as dark urine and pale stools remain often unrecognised. The reported stool colour in the history taking from parents is often unreliable. Late referral can be due to a delayed or inadequate follow-up of newborns in the primary health care system. Following the health care

visit at the age of 2 weeks, the next visit is often planned at the time of the first immunisations (6–8 weeks).

In order to tackle the problem of late referral, several measures can be taken. The knowledge of primary health care providers about neonatal cholestasis has to be improved, and parents should be informed about prolonged jaundice and the importance of stool and urine colour. A health care visit after the 2-week visit scheduled at the age of 4 weeks (and not postponed till the age of 6–8 weeks) also allows earlier identification of children at risk. In neonatal jaundice, the urine should be tested for bilirubin and stools seen by the health care providers themselves. A mass screening method for early diagnosis of biliary atresia using stool colour cards has been proven to be efficient in Japan and Taiwan [6, 16, 17]. Despite the rarity of cholestasis, every newborn presenting with jaundice beyond the age of 2 weeks should be evaluated for cholestasis and therefore a fractionated bilirubin has to be checked. In case the conjugated bilirubin is elevated, urgent referral for further diagnostic investigations is indicated.

The first step, along with a thorough history taking and clinical examination, should be the evaluation of coagulation by measuring the prothrombin time or international normalised ratio (INR), followed by administration of parenteral vitamin K if coagulopathy is present. The severity of liver dysfunction needs to be assessed, and immediately, life-threatening conditions or disorders requiring urgent specific treatment such as galactosaemia must be looked for (Fig. 1). Coagulopathy unresponsive to parenteral vitamin K administration indicates acute liver failure, and referral to an intensive care facility in a paediatric hepatic transplantation centre is mandatory.

Irrespective of age, repeated unpigmented stools are always pathologic: if consecutive stools over a course of 2 to 3 days contain no green or yellow pigment in infants, biliary atresia should be ruled out. Any child presenting with acholic stools should therefore be referred early to a paediatric hepatology unit for further diagnostic work-up. This work-up will most often include a liver biopsy. If typical histologic findings for biliary atresia are present, intraoperative cholangiography is usually performed to confirm this diagnosis before proceeding to Kasai porto-enterostomy.

History and physical examination

Both history and physical examination may provide important diagnostic clues.

The evaluation should include details of family history, asking for consanguinity, birth history and early neonatal course. The obstetric history may reveal maternal infection (e.g., TORCHES, hepatitis B) or cholestasis of pregnancy (which may be associated with progressive familial intrahepatic cholestasis).

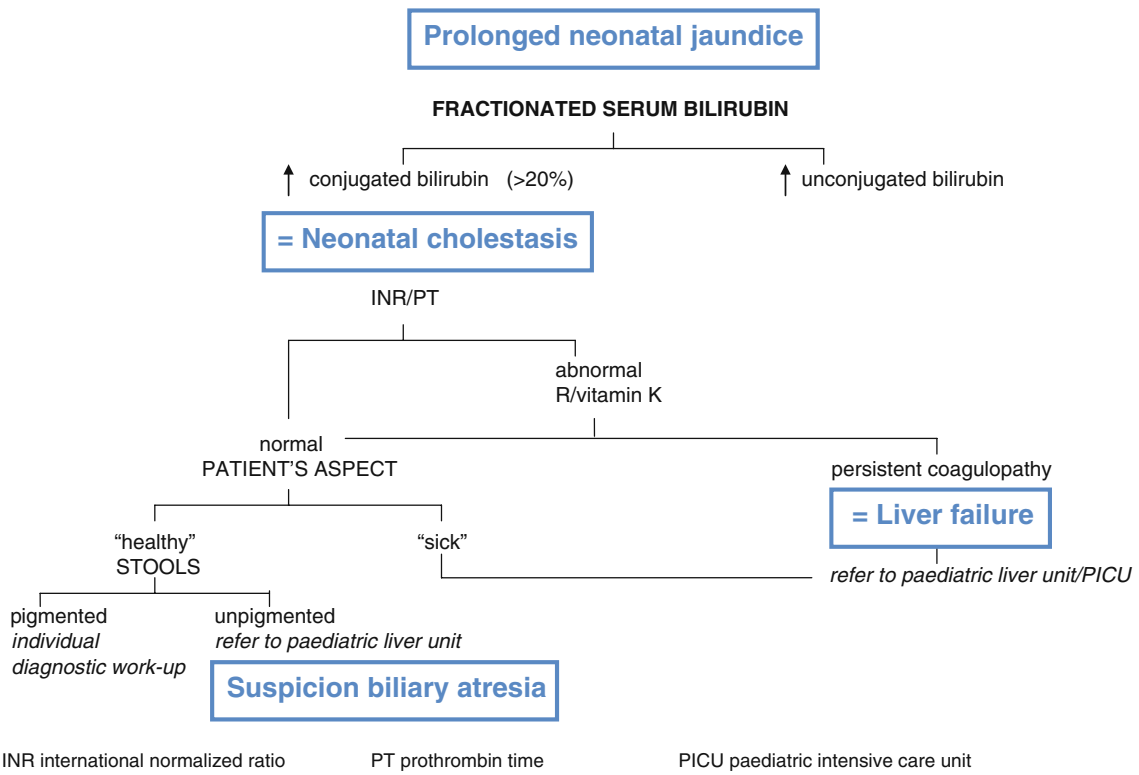

Fig. 1 Decision tree for neonatal cholestasis

Irritability, poor feeding, vomiting and lethargy can be seen in generalised infections or metabolic disorders such as galactosaemia and tyrosinaemia.

Dysmorphic facial features and other congenital anomalies occur in Alagille syndrome or other chromosomal defects. Congenital malformations such as cardiac anomalies, polysplenia, intestinal malrotation and situs inversus may be found in children with biliary atresia [5]. Congenital infections are associated with microcephaly, low birth weight, growth restriction, chorioretinitis, purpura and bleeding from thrombocytopenia. Ascites, oedema and coagulopathy not responsive to vitamin K administration indicate impairment of hepatic synthetic function. In an acutely ill child, sepsis, shock, heart failure, hypopituitarism and metabolic disorders such as galactosaemia or tyrosinaemia should promptly be looked for.

Infants with neonatal cholestasis might initially be evaluated because of signs of increased bleeding tendency such as gastrointestinal blood loss, bleeding from the umbilical stump, intracranial haemorrhage or bruising as a consequence of vitamin K deficiency.

Hepatomegaly is often present. The spleen may be enlarged with infection or as a result of advanced prenatal liver disease and fibrosis but is usually of normal size in the initial course of extrahepatic biliary obstruction [25].

Dark urine is a non-specific indicator of conjugated hyperbilirubinaemia. The presence of acholic stools (Fig. 2) is suggestive, but not diagnostic of extrahepatic biliary obstruction, since this can also be present in severe intrahepatic cholestasis. The presence of pigmented stools, on the other hand, suggests patency of the extrahepatic biliary tree and generally makes biliary atresia unlikely [7].

However, in the early course of biliary atresia, stools may appear normally or intermittently pigmented. Furthermore, in case of severe cholestasis, peeling-off of bile-tinged colon mucosa can give some pigment to the outer surface of the stools.

Fig. 2 The presence of acholic stools

It is therefore extremely important in the evaluation of cholestatic infants that stool colour is assessed at several occasions by an experienced person as parents do not appear to be reliable observers of stool colour [16, 17, 21].

Ocular assessment is part of the clinical evaluation of cholestatic infants. Ocular manifestations which can be found are posterior embryotoxon in Alagille syndrome, optic nerve hypoplasia which can be associated with panhypopituitarism, chorioretinitis in congenital infections, cataract in intra-uterine infections or galactosaemia and ocular coloboma in Cat Eye syndrome [9].

Cardiac evaluation can reveal peripheral pulmonary stenosis or other cardiac anomalies in Alagille syndrome, dextrocardia in biliary atresia or patent ductus arteriosus or septum defects in congenital infections.

Laboratory examination

The most important initial investigation is to confirm cholestasis by fractionated serum bilirubin levels and to establish the severity of liver dysfunction by assessing hepatic synthetic function (INR or prothrombin time, albumin, serum glucose levels, ammonia). When the INR is abnormal, parenteral vitamin K has to be administered immediately. Coagulation studies should normalise within hours after administration of vitamin K when the parenchymal liver function is normal. Poor synthetic function including hypoglycaemia and coagulopathy unresponsive to parenteral vitamin K administration signifies acute liver failure. No reliable laboratory or imaging test is available which differentiates biliary obstruction from other causes of neonatal cholestasis.

The serum transaminases (ALT and AST) are sensitive indicators of hepatocellular injury but lack specificity or prognostic value.

Elevated levels of alkaline phosphatase can be seen in biliary obstruction, but this again is a non-specific finding as this enzyme is present in liver, bone and kidney. Gamma glutamyl transpeptidase is a sensitive marker of biliary obstruction. This enzyme which is located in the epithelium of the biliary tree and canaliculi is elevated in most cholestatic disorders. Paradoxically low or normal levels are found in some patients with progressive familial intrahepatic cholestasis and disorders of bile acid metabolism [19].

Because it can be very difficult to distinguish α1-antitrypsin deficiency from extrahepatic biliary atresia based on clinical and histologic findings, it is essential to rule out α1-antitrypsin deficiency before sending a child to theatre for hepatobiliary surgery. Serum concentrations

of α1-antitrypsin, however, can be misleading as they may increase as a response to inflammation, even in homozygous PiZZ individuals, giving a falsely reassuring impression. Therefore, α1-antitrypsin deficiency can only be ruled out by determining the α1-antitrypsin phenotype (by isoelectric focusing, agarose electrophoresis at acid pH) or genotype [23].

A more detailed overview of diagnostic laboratory testing in neonatal cholestasis, including metabolic tests, can be found in textbooks on paediatric hepatology [7, 25].

Ultrasonography

Abdominal ultrasound is an important tool in the diagnostic work-up of neonatal cholestasis and should always be performed before a liver biopsy is considered. It is a useful test to identify for instance a choledochal cyst, gall stones, sludge in the biliary tree or gallbladder. A small or absent gallbladder is suggestive but not diagnostic for biliary atresia and the presence of a normal gallbladder, on the other hand, does not exclude biliary atresia either. The finding of the triangular cord sign (an echogenic area at the *porta hepatis*) is believed to be a specific finding of biliary atresia [22].

Radionuclide imaging

Hepatobiliary scintigraphy using technetium-labeled iminodiacetic acid analogues has been used to differentiate biliary atresia from nonobstructive causes of cholestasis. Although the sensitivity for the diagnosis of biliary atresia is high, specificity is low, and tracer excretion is absent in many patients in the absence of anatomic obstruction. As this test is expensive, time consuming and poorly specific, hepatobiliary scintigraphy adds little to the routine evaluation of the cholestatic infant [21].

Magnetic resonance cholangiopancreatography

Insufficient data are available to recommend magnetic resonance cholangiopancreatography as a routine investigation for neonatal cholestasis [21]. In experienced hands, it might be a useful tool in the evaluation of certain individual cases.

Liver biopsy

Percutaneous liver biopsy is the investigation with the highest diagnostic usefulness in neonatal cholestasis. The diagnostic accuracy for biliary atresia in several studies was more than 90% [19].

The typical histologic findings in extrahepatic bile duct obstruction include bile duct proliferation, bile plugs in small bile ducts, portal tract oedema and fibrosis.

However, when the biopsy is done early in the course (before 6 weeks of age), these findings may not all be present and repeat biopsy may be required. Liver biopsy can also be diagnostic for other specific conditions or can reveal non-specific findings which are helpful in guiding further diagnostic work-up (e.g., microvesicular steatosis pointing in the direction of metabolic liver disease).

In addition to conventional histology, immunohistochemical methods, electron microscopy and biochemical and molecular assays can be performed on the liver tissue [19]. A liver biopsy is recommended in infants with undiagnosed cholestasis and should be interpreted by a pathologist with experience in paediatric liver disease [21].

Medical management

As stated above, the first goal in managing children with cholestasis is the recognition of diseases amenable to specific medical therapy (e.g., galactosaemia, tyrosinaemia, hypothyroidism) or early surgical intervention (biliary atresia, choledochal cyst). In most other cases, medical management is mainly supportive aiming for optimal growth and development and treating the complications such as fat malabsorption and fat-soluble vitamin deficiencies, pruritus, hypercholesterolaemia, cirrhosis, portal hypertension and liver failure.

In the presence of steatorrhoea and increased energy expenditure, caloric intake should be approximately 125% of the recommended dietary allowance based on ideal body

Table 2 Suggested supplementation of fat-soluble vitamins, further adjustments are made based on serum fat-soluble vitamin levels

	Preparation	Initial dose
Vitamin A	Water-dispergible preparation	5,000 U/day PO
Vitamin D	Cholecalciferol	800 U/day PO
Vitamin E	D-α-tocopheryl polyethylene glycol 1,000 succinate	15–25 U/kg/day PO
Vitamin K	Phytomenadion	2.5–5 mg 2×/week PO 2–5 mg 1×/month IM

PO orally, *IM* intramuscularly

weight. Infant formulas containing medium chain triglycerides (MCTs) will provide better energy balance. Because they are relatively water soluble, MCTs do not require solubilisation by bile acid micelles and can be directly absorbed in the portal circulation. Aggressive nutritional therapy is essential for those children who will eventually require liver transplantation as this may improve their chances for a successful operation as well as normal growth and development following transplantation.

When cholestasis begins in infancy, depletion of the limited body stores of fat-soluble vitamins present at birth occurs rapidly if supplementation is not initiated. Special formulations of these vitamins have been developed, less dependent on the presence of bile acids for absorption than standard formulations. The preparations and initial doses of fat-soluble supplements used in our institution in cholestatic neonates are summarised in Table 2. Blood vitamin levels and clinical signs of deficiency should be monitored closely, and subsequent dose adjustments should be made in order to prevent both under- and overdosing.

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