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Case Series

Clinical, laboratory, and etiological profile of three infants with neonatal cholestasis and review of literature

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ABSTRACT

Neonatal cholestasis occurs due to failure of the excretion of bile. This happens due to defects in intrahepatic bile production, defects in transmembrane transport of bile, or mechanical obstruction to the flow of bile. Etiology varies from biliary atresia, choledochal cyst, inborn errors of metabolism, neonatal hepatitis, progressive familial intrahepatic cholestasis, congenital infections, etc. Our 3 patients presented with hepatomegaly, splenomegaly, pale stools, and dark urine. We hereby report all these Indian infants presented with cholestasis and discussed in detail regarding clinical, laboratory, and etiological profiles of all.

Keywords: Cholestasis, Biliary atresia, Infections, Toxoplasmosis, Cytomegalovirus

INTRODUCTION

Neonatal cholestasis is generally defined as conjugated hyperbilirubinemia that manifests during the infantile period. Cholestasis results from diminished bile formation and/or excretion, which can be caused by several clinical conditions.[1] Cholestatic jaundice affects approximately 1 in every 2,500 infants.[2] Structural defects include biliary atresia and choledochal cyst among which biliary atresia is somewhat more commonly seen. metabolic disorders such as tyrosinemia, galactosemia, and hypothyroidism; inborn errors of bile acid metabolism; Alagille syndrome; neonatal hepatitis; infection including congenital toxoplasmosis and cytomegalovirus sepsis; and other rare disorders including PFIC (progressive familial intrahepatic cholestasis), panhypopituitarism, Caroli's disease, and cystic fibrosis.[2] Persistently pale color stools, high-colored urine, and organomegaly are common findings. Other disease-specific presentations are also seen, like galactosemia present with oil droplet cataract, hypoglycemia, and *E. coli* sepsis, tyrosinemia present with neonatal cholestasis, renal tubular acidosis, and neonatal liver failure, Alagille syndrome show syndromic facies, structural defects, and posterior embrytoxon on ophthalmic evaluation.[3-5] That's why a detailed evaluation of all systems require for the etiological diagnosis of neonatal cholestasis. Though surgical, metabolic defects and neonatal hepatitis more are likely to cause neonatal cholestasis. We hereby report 3 cases of neonatal cholestasis that presented at a tertiary pediatrics care hospital in central Gujarat India during their infancy, causative etiology behind their cholestasis turns out to be congenital cytomegalovirus (CMV), congenital toxoplasmosis and surprisingly third infant had biliary atresia and along with CMV sepsis.

CASE SERIES

Case 1

A 5-month-old boy presented with complaints of passing clay-colored stools since birth; abdominal distension, yellowish discoloration of skin, and sclera since 2 months of age. No significant family history was noted. On general examination the patient was irritable. On head-to-toe examination, yellowish skin discoloration, sclera, and

microcephaly were noted. On systemic examination, hepatomegaly (9 cm) and splenomegaly (10 cm) were noted. On further investigation, an ultrasonography of the abdomen was done which showed hepatosplenomegaly. Ophthalmological and hearing assessment was done, which was normal. Blood investigation showed direct hyperbilirubinemia with altered liver enzymes, and the coagulation profile was normal. We investigated the patient for congenital infections, which were suggestive of CMV infection (Ig M positive) and confirmed by urinary CMV-PCR. Definitive treatment was started in form of intravenous Gancyclovir and other supportive management. The patient's general and clinical condition improved after treatment.

Figure 1: Infant with neonatal cholestasis having yellowish discoloration of skin as well as the organomegaly.

Case 2

A 5-month-old female presented with complaints of yellowish discoloration of the skin, abdominal distension since 1 month of age; and passing clay-colored stools on and off since birth. There was no significant family history. On general examination, icterus was noted on the sclera. On systemic examination, hepatomegaly (6 cm) and splenomegaly (7 cm) were noted. The patient's ultrasonography showed hepatosplenomegaly with a normal gall bladder. On investigations, direct bilirubinaemia, altered liver enzymes, and a deranged coagulation profile were noted. Ophthalmological and hearing examinations were normal. On further evaluation for congenital infections, TORCH titre was done, which turned out to be positive for Toxoplasma antibody (toxoplasma IgM antibody 19.2 AU/ml and toxoplasma IgG antibody >400 IU/ml). A CT scan head was done and no calcifications were noted. On definitive management, the patient had been started with a sulfamethoxazole and trimethoprim combination due to the unavailability of sulfadiazine and pyrimethamine. Coagulopathy was corrected with vitamin K and the patient received supportive treatment.

Figure 2: Infant with neonatal cholestasis showing abdominal distension.

Case 3

A 4-month-old female presented with abdominal distension, umbilical hernia, passing clay-colored stool, and high-colored urine since birth. On general examination, microcephaly was noted. Yellowish discoloration of skin and sclera was noted. The patient had an umbilical hernia. On systemic examination hepatomegaly (7 cm) and splenomegaly (6 cm) were noted. Ophthalmological and hearing assessment was normal. On investigation, conjugated hyperbilirubinemia with altered liver enzymes and an altered coagulation profile was noted. The patient was evaluated for structural causes. CECT abdomen was done, which showed hepatomegaly with atretic gall bladder suggestive of biliary atresia and left multicystic dysplastic kidney. On the congenital infection screening test, the cytomegalovirus IgM antibody was positive. Coagulopathy was corrected with vitamin K. The patient was supplemented with fat-soluble vitamins double the RDA dosage. We sent the patient for further management to the pediatric surgery centre.

Table 1: Clinical, biochemical, serological, and etiological comparison between three patients.

Variables	Case 1	Case 2	Case 3
Age (Months)	5 months	5 months	4 months
Clinical presentation	Clay-colored stools, abdominal distension, yellowish discoloration of the skin, and sclera	Yellowish discoloration of skin and sclera, abdominal distension; and passing clay-colored stools on and off since birth	Abdominal distension, umbilical hernia, passing clay-colored stool, and yellowish discoloration of sclera and urine
Birth history	Not significant	Not significant	Not significant
Findings	Hepatomegaly, splenomegaly microcephaly	Hepatomegaly, splenomegaly	Umbilical hernia, hepatomegaly splenomegaly microcephaly
Ophthalmological evaluation	Normal	Normal	Normal
Serum bilirubin (mg/dl) total/direct/indirect	26/16.3/9.7	25/16.8/8.2	6.4/3.7/2.7
Liver enzymes SGPT/SGOT/ALP (IU/l)	149/84/776	202/500/626	100/205/504
Coagulation profile PT/APTT/INR (sec)	13.8/33.9/1.04	48.4/74/3.77	55/59.5/4.41
Ultrasonography abdomen	Hepatosplenomegaly, gall bladder appeared normal	Hepatosplenomegaly, gall bladder appeared normal	Hepatomegaly, biliary atresia and left multicystic dysplastic kidney
Serological tests	CMV IgM antibody positive with urinary CMV assay positive	Toxoplasma IgM antibody positive	CMV IgM antibody positive
Management	Intravenous ganciclovir and fat-soluble vitamin supplements	Sulfamethoxazole plus trimethoprim combination and fat-soluble vitamin supplements	Referred to higher centre for surgical management and fat-soluble vitamin supplements

DISCUSSION

Cholestasis in infancy is defined as serum direct bilirubin level >1 mg/dL and > 20% of the total bilirubin. Although historically 2 mg/dL had been arbitrarily used as a threshold for direct bilirubin, this has recently been reduced to 1 mg/dL.[1,6] Jaundice beyond 2 weeks of age in a breastfed infant should be evaluated.

If direct hyperbilirubinemia is identified, further evaluation for hepatobiliary causes should take precedence. Diagnostic pathway for neonatal cholestasis has evolved in recent years, largely because of expanding identification of new genetic causes of cholestasis, advent of next-generation sequencing to identify genetic variants, and introduction of enzymatic studies.[7]

Table 2: Causes of neonatal cholestasis.[7]

Causes of neonatal cholestasis	
Anatomical	Biliary atresia
	Choledochal cyst
	Cholelitiasis
	Biliary sludge
	Inspissated bile
	Spontaneous perforation of the common bile duct
	Tumor
Infections	Congenital viral
	Bacterial
	Spirochete
	Parasites
Toxins	Drugs
	Endotoxin
	Total parenteral nutrition-associated cholestasis
	Herbal products

Continued.

Causes of neonatal cholestasis	
Endocrine	Hypothyroidism
	Panhypopitutarism
Immune	Gestational alloimmune liver disease
Genetic and inborn errors of metabolism	Alpha 1 antitrypsin deficiency (SERPINA1)
	Alagille syndrome (JAGGED1, NOTCH2)
	Arthrogryposis/renal/cholestasis (VPS33B, VIPAR)
	Congenital hepatic fibrosis (PKHD1)
	Citrin deficiency (Adult citrillinemia type 2) (SLC25A13)
	Cystic Fibrosis (CFTR)
	Bile acid synthesis defects (AKR1D1, AMACR, CYP7B1, HSD3B7, CYP7A1, CYP27A1)
	Bile Acid conjugation defects (BAAT, SLC27A5)
	Fatty acid oxidation defects (SCAD, LCAD)
	Galactosemia (GALT)
	Glycogen storage disease type IV (GBE1)
	Hereditary fructose intolerance (ALDOB)
	Mitochondrial respiratory chain disorders (DGUOK, MPV17, POLG)
	Neonatal ichthyosis sclerosing cholangitis syndrome (CLDN1)
	Neonatal pick type C disease (NPC1, NPC2)
	Peroxismal disorders (PEX1, PEX6, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX7)
	Progressive familial intrahepatic cholestasis
	Bile transport defects (ATP8B1, ABCB11, ABCB4, NR1H4, OSTα/β, WDR83OS, ABCC12)
	Cytoskeleton defects (TJP2, MYO5B, UNC45, USP53, KIF12, PLEC)
	Other defects (LSR, PPM1F)
	Smith Lemli Opitz syndrome (DHCR7)
	Lipid storage diseases (SCP2)
	Tyrosinemia type 1 (FAH)
	Urea cycle defects
Others	Idiopathic neonatal hepatitis (Transient neonatal cholestasis),
	Ischemia
	Hypoxia
	Hepatic congestion
	Hemophagocytic lymphohistiocytosis (HLH)
	Malignancy

The presentation of neonatal cholestasis is protean, extending across yellowish discoloration of the skin to acute liver failure and death. A thorough head-to-toe examination is a must for any case of neonatal cholestasis. Acholic stools and high-colored urine are the characteristic terms used to describe an infant with cholestasis.[1] An infant may likewise present with bleeding diathesis; pruritis; deficiency of vitamins A, D, E, and 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 (neonatal hemochromatosis). Splenomegaly can be seen in infants who have cirrhosis and portal hypertension, intrauterine infections, storage diseases, and hemolytic disorders such as Rh-isoimmunization.[7] Chorioretinitis is regularly associated with intrauterine infections. Congenital infections may also be associated with rash, microcephaly, intrauterine growth restriction, and intracranial calcification. Facial dysmorphism may suggest chromosomal abnormality/ Alagille syndrome.[1,5]

A palpable mass in the upper quadrant of the abdomen may indicate a choledochal cyst. A cardiac murmur increases the likelihood of Alagille syndrome or biliary atresia.[2] Congenital CMV presents with small for gestational age (SGA) neonate, microcephaly, petechiae or purpura, blueberry muffin rash, and cholestasis. Neurologic signs (lethargy, hypotonia, seizures, poor sucking reflex). The mode of transfusion in congenital CMV is perinatal, transplacental, and postnatally from infective body fluids like saliva, urine, and breast milk, and a blood transfusion from infective individuals. Most congenitally infected children are asymptomatic at birth, they may develop some symptoms later in life. Loss of vision is the most common (up to 95%) sequel in congenitally infected children. Hydrocephalus, chorioretinitis, intracerebral calcification, mental retardation, loss of hearing, and rarely neonatal cholestasis. Transplacental toxoplasma infection occurs when an uninfected mother acquires the infection during pregnancy, there are other rare modes of transmission such as through organ transplantation, blood transfusion,

and laboratory-acquired toxoplasmosis.[6] On physical examination, infants with biliary atresia are generally thrive 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. By contrast, infants with infectious and metabolic causes appear sick and have inadequate weight gain. A particular odor of the body or urine may point to a metabolic cause. Examination of male genitalia and the ability to fix and follow a moving object may be useful clues for panhypopituitarism and septo-optic dysplasia.[7]

Diagnostic approach

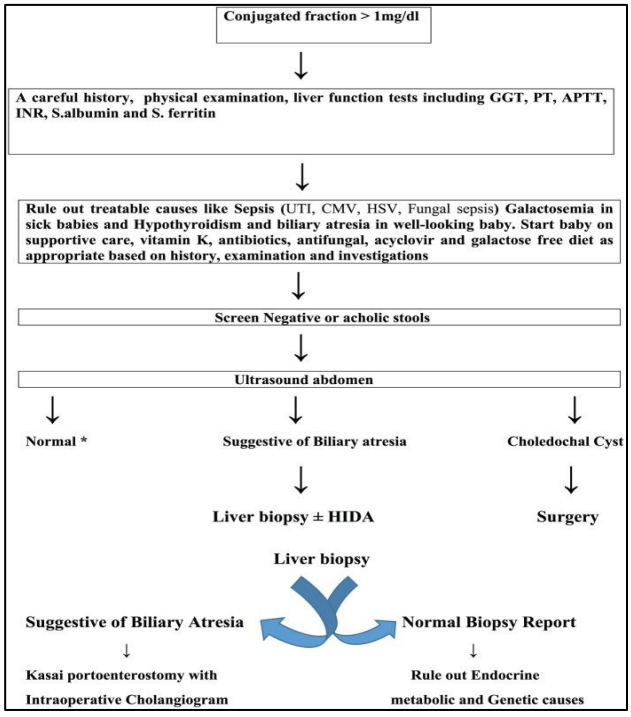

Figure 3: An approach to diagnosis and management of neonatal cholestasis.[3,4,7]

CONCLUSION

Neonatal cholestasis must be considered in any infant presenting with prolonged jaundice longer than 2 weeks or early if associated with hepatomegaly, failure to thrive, acholic stools, or dark urine. Neonatal cholestasis, although rare, it is a life-threatening condition unless timely diagnosed and managed appropriately. However, delay in diagnosis of cholestasis, particularly of biliary atresia, remains a problem. Misinterpretation of physiological jaundice, lack of national-level screening programs for inborn errors of metabolism, limited genetic study resources, and presence of pigmented stools are often the cause of delay in diagnosis. There is a need for strict follow-up, the use of stool cards, and awareness. Even if there is no specific management for each cause, a few causes like biliary atresia and congenital infections have a definitive line of management. Appropriate supportive care and nutritional rehabilitation may be life-saving in most cases of neonatal cholestasis. Early screening for congenital infections and structural causes is recommended, as early diagnosis of biliary atresia and timely intervention shows higher chances of survival. Similarly, late detection and treatment of CMV and toxoplasma show poor response to treatment and overall poor prognosis.

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