Review :

Jaundiced baby- what should I do as a pediatrician?

Borkar VV*, Sachade V*, Mohanka R, Shah S*.**

Department of Hepatology*, Hepatobiliary Surgery and Liver Transplantation**, Global Hospital, Parel, Mumbai 400012

Email - vibhor.borkar@gmail.

Abstract:

Neonatal cholestasis is an emergency situation. Many of these cases are still diagnosed late and inadequately treated. Biliary atresia is most common condition which presents as neonatal cholestasis. Prompt detection of a case, a guided investigational approach, specific management and timely referral is very crucial. A concise review is presented for a pediatrician to guide about the appropriate measures to be taken to offer the best possible outcome for a neonate with cholestasis.

Key words:

Neonatal cholestasis, biliary atresia, approach

Abbreviations:

INH- Idiopathic neonatal hepatitis, GGT- gamma-glutaryl transferase, INR- internationally normalized ratio, CMV- cytomegalovirus, PFIC- progressive intrahepatic familial cholestasis.

Inroduction:

Jaundice is a common problem in newborn affecting almost 25-30% of near term babies. However, majority of them have transient unconjugated hyperbilirubinemia due immaturity of hepatic enzyme glucuronyltransferase. A small portion of them had cholestasis. Neonatal cholestasis means decrease in bile flow and elevation of conjugated bilirubin. Conjugated hyperbilirubinemia is generally defined as a conjugated or direct bilirubin level greater than 1 mg/dL when the total bilirubin is less than 5 mg/dL or more than 20% of the total bilirubin if the total bilirubin is greater than 5 mg/dL.1 Conjugated hyperbilirubinemia is never physiologic or normal. Cholestatic jaundice is seen in 1 in 2500 in western countries and 26% of all chronic liver disease in children from India.2 The process occurs as a result of impaired bile formation by the hepatocytes or from obstruction to the flow of bile through the intrahepatic and/ or extrahepatic biliary tree. In the neonate, the clinical and laboratory features of the many liver diseases presenting with cholestasis are quite similar. An important focus in approaching neonatal cholestasis is a prompt differentiation between intrahepatic and extrahepatic cholestasis and, if possible, to establish a specific diagnosis. Most of the neonates with biliary atresia appear well except jaundice. This lures parents and physician to delay the investigations. Extrahepatic cholestasis like biliary atresia is amenable to surgical correction and early surgery (within 8 weeks) is extremely important for successful bile drainage and prolonged survival. Mieli-Virgani et al demonstrated that more than 80% babies with BA became jaundice free when the portoenterostomy was done before 60 days of age, while the success rate of establishing biliary drainage dropped to 25-35% only when the surgery was done after 60 days of age.3

No screening test can predict which infant will develop cholestasis. So, detection of cholestasis depends on clinical recognition of yellow colored eyes, diaper staining (dark colored urine) and/ or pale stools by parents. Causes of cholestasis in younger infants (< 2 months of age) are mentioned in table 1. A cost-effective, quick, simplified and appropriate management protocol of

neonatal cholestasis in developing countries was published in Indian Pediatrics.4 The number of distinct diseases presenting as cholestasis is greater in neonates than at any other time of life. So-called Idiopathic neonatal hepatitis (INH) was the most common diagnosis. But in recent era with new diagnostic modalities available, the diagnosis of INH is decreasing and rarer diseases are becoming more common. There is no alternative to a thorough clinical history and physical examination, which can give many diagnostic clues. Observing the stool color of each baby is very important. All babies while being discharged after birth should have a documentation of their stool color in the discharge card. In Taiwan, a national screening program has been implemented through which an infant stool color card is placed into the child health booklet given to every neonate. This program has increased the national rate of the Kasai operation performed before 60 days of age from 49% to 66%, and it has increased the 3-month jaundice-free rate after the Kasai operation from 35% to 61% ($p < 0.001$). In addition, the 5-year jaundice-free survival rate with native liver increased from 27% to 64% ($p < 0.001$) and the 5-year overall survival rate increased from 56% to 89% ($p < 0.001$).5 Such a national effort is grossly lacking in India. A child with suspected neonatal cholestasis should first have a liver function test including gamma-glutaryl transferase (GGT) and internationally normalized ration (INR) (after vitamin K). A presence of persistent clay colored stool has 79% accuracy of diagnosing biliary atresia.6 After confirmation of conjugated hyperbilirubinemia, synthetic function (normal or delayed INR), clinical status (as sick or stable); the baby should be evaluated as per the focused and rapid investigational approach (Figure 1).4 Ultrasonographic evaluation of liver should be specifically looked for gall bladder contractility, triangular cord signs, dilatation of biliary system, splenic malformations, inspissated bile, any features of cirrhosis, collaterals and ascites. Liver biopsy plays a very crucial role in diagnosing biliary atresia with sensitivity and specificity of 88.2 each.7 A nuclear scan is useful to exclude biliary atresia rather than diagnosing it. Features of biliary atresia which are found on liver biopsy are portal tract widening, portal tract fibrosis, bile ductular plugs and bile ductular proliferation.7 Apart from biliary atresia, many other diseases like progressive familial cholestasis, Alagille syndrome, congenital hepatic fibrosis, Niemann-pick disease, cytomegalovirus (CMV) hepatitis, Alpha-1 antitrypsin deficiency. A clue to a possible metabolic disease can be picked up by finding micro vesicular hepatic steatosis. Any sepsis should be treated promptly and etiological work-up should be initiated. In a baby with neonatal cholestasis with cirrhosis, always suspect biliary atresia, Galactosemia, Tyrosinemia, progressive intrahepatic familial cholestasis (PFIC)-2, bile acid synthetic disorders. For a neonatal cholestasis with deranged INR, one should think of metabolic disorders like Galactosemia, Tyrosinemia, and neonatal hemochromatosis. In a baby suffering for neonatal cholestasis with ascites, one should look for Galactosemia, Wolman's disease, Tyrosinemia, spontaneous perforation of bile ducts. The etiology wise work up is listed in table 2.

Even if the specific diagnosis or treatment is not possible, infants with progressive liver disease usually benefit from optimal nutritional support and medical management of complications of cholestasis and possibly cirrhosis until liver transplantation is performed. Sufficient calories and protein intake (Calories- 125 % of the RDA and protein 2-3 g/kg/ day) along with medium chain triglycerides (MCT) oil should be given. The optimum nutritional management is summarized in table 3.8 Specific management of individual condition is summarized in table 4. It's worthwhile to note that many of these are treatable.

To summarize, neonatal cholestasis is an emergency condition and prompt investigation and referral is must. A suspected case of biliary atresia must be picked up and diagnosed before 4-6 weeks of age and should be offered Kasai portoenterostomy. Apart from biliary atresia, many of the conditions are treatable and warrants

complete investigation.

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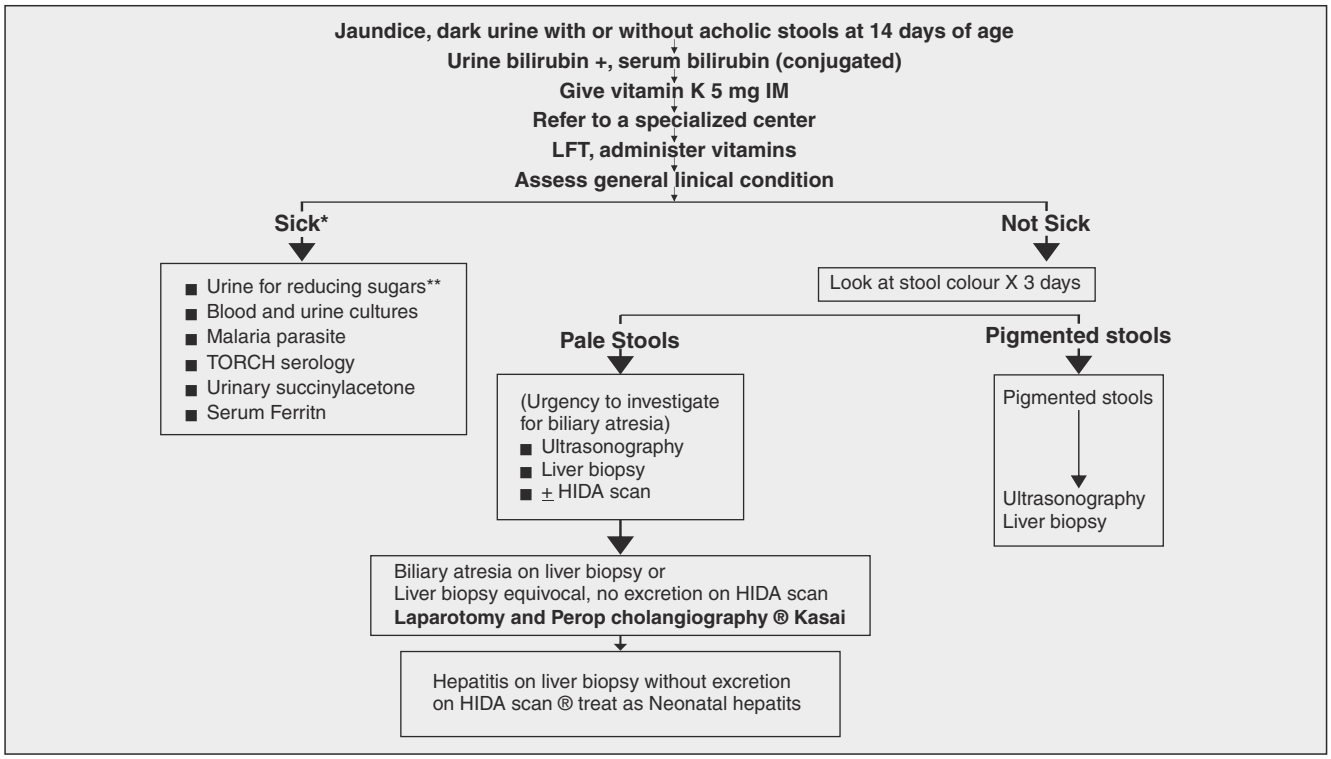

Table 1- Causes of cholestasis in younger-than-2 months-old infant

Obstructive cholestasis	Hepatocellular cholestasis
Biliary atresia	Idiopathic neonatal hepatitis
Choledochal cyst	Viral infections- Cytomegalovirus
Alagille syndrome	Bacterial infection- Urinary tract infection, sepsis, syphilis
Inspissated bile	Genetic/metabolic disorders
Gallstones or biliary sludge	1-antitrypsin deficiency, Tyrosinemia, Galactosemia Hypothyroidism
Neonatal sclerosing cholangitis	Progressive familial intrahepatic cholestasis
Congenital hepatic fibrosis/ Caroli's disease	Bile acid synthesis disorders
	Cystic fibrosis
	Storage disorders- Niemann pick disease, Wolman's disease
	Pan hypopituitarism
	Toxic/secondary
	Parenteral nutrition-associated cholestasis
	Hemophagocytic lymhohistiocytosis

Table 2: Etiology wise diagnosis of common causes of Neonatal cholestasis

Condition	Suggested investigations
Biliary atresia	Ultrasonography, Liver biopsy Peroperative/ laproscopic cholangiogram (Gold standard)
Choledochal cyst	Ultrasonography followed by MRCP
Toxoplasmosis	IgM-specific antibodies
Rubella	IgM-specific antibodies
Cytomegalovirus	IgM antibodies, Urine for viral culture, PCR
Herpes simplex	viral culture/ electron microscopy of vesicle scraping
Syphilis	VDRL, FTA-ABS, long-bone films
Giant cell hepatitis	Liver biopsy
?1 -Antitrypsin deficiency	Serum ?1 -Antitrypsin concentration, PI type
Galactosemia	Galactose-1-phosphate uridylltransferase
Tyrosinemia	Serum tyrosine, methionine, ?-fetoprotein, urine succinylacetone, USG- Nephromegaly
Neonatal hemochromatosis	Serum ferritin, transferrin saturation, buccal mucosa biopsy, MRI abdomen
Hereditary fructosemia	Liver biopsy: EM, enzyme activities
Citrin deficiency; citrullinemia, type II	Serum amino acids; genetic testing
Niemann-Pick, type A	Bone marrow aspirate, sphingomyelinase
Niemann-Pick, type C	Storage cells in bone marrow aspirate, liver, rectal biopsy, fibroblast studies
Wolman disease	Abdominal radiography of adrenal glands,
Bile acid synthesis defects	Urinary bile acid intermediates by FAB-MS, total serum bile acids
Progressive familial intrahepatic cholestasis	GGT, total serum bile acids, genetic testing, Immunohistochemistry on liver histology
Cystic fibrosis	Sweat chloride test, MRCP, Mutation analysis
Zellweger syndrome	Very-long-chain fatty acid studies
Idiopathic Neonatal cholestasis	Diagnosis of exclusion

MRCP- magnetic resonant cholangio-pancreaticography, IgM- Immunoglobulin M, PCR- polymerase chain reaction, VDRL- veneral disease research laboratory, FTA- ABS- EM- electron microscopy, MRI- magnetic resonance imaging, GGT- gamma glutaryl transferase, FAB-MS

Table 3: Optimal nutritional management of a child with neonatal cholestasis

Medication	Route
Vitamin A	Oral 5000-25,000 IU/d
Vitamin D	Oral 400-1200 IU/d
Vitamin E	50-400 IU/ day
Vitamin K	Oral 2.5 twice/week to 5 mg Parenteral 2-5 mg IM, SC or IV 4 weekly
Water soluble vitamins	Oral 1-2 times the RDA
Calcium	Oral 20-100 mg/kg/d
Phosphorus	Oral 25-50 mg/kg/d
Zinc	Oral 1 mg/kg/d
Magnesium	Oral 1-2 mEq/kg/d Intravenous 0.3-0.5 mEq/ kg over 3 hours of 50% solution
Elemental iron	5-6 mg/kg/day

Table 4: Specific management of Neonatal cholestasis

Condition	Treatment
Biliary atresia	Kasai portoenterostomy (if < 120 days) Liver transplantation if failed or missed procedure
Choledochal cyst	Cyst resection and Hepatico-jejunostomy
Toxoplasmosis	Spiramycin
CMV hepatitis	Gancyclovir if severe
Herpes simplex hepatitis	Acyclovir
Galactosemia	Galactose free formula
Tyrosinemia	Nitinisone and low tyrosine formula
Neonatal hemochromatosis	Antioxidant cocktail, immunoglobulins, Liver transplantation
Hereditary fructose intolerance	Fructose/ sucrose-free diet
Citrin deficiency	Lactose free low protein high carbohydrate diet
Bile acid synthetic defects	Bile acid supplementation
Progressive familial intrahepatic cholestasis	Management of pruritus, Biliary diversion procedures, Liver transplantation
Alagille syndrome	Management of pruritus, hypertriglyceridemia, pulmonary hypertension,
TPN associated cholestasis	Enteral feeding, metronidazole, Ursos-deoxy-cholic acid