

LEADING ARTICLE

Neonatal Cholestasis: An Update

Syed Shafi Ahmed

Introduction

Cholestatic jaundice in infancy is an uncommon but potentially serious problem that indicates hepatobiliary dysfunction.¹ Neonatal cholestasis (NC) can be defined as conjugated hyperbilirubinemia in the 1st 90 days of extra-uterine life that occurs when conjugated bilirubin is higher than 1 mg/dl, if the total serum bilirubin is ≤ 5 mg/dl, or $>20\%$ of total serum bilirubin when it is >5 mg/dl. Conjugated hyperbilirubinemia at any age in a newborn is pathological and requires evaluation.²⁻⁴

Incidence

NC affects 1 in 2500 infant in the west. In India, it constitutes 19% to 33% of all chronic liver disease in children reporting to tertiary care hospitals.⁵⁻⁸ Idiopathic neonatal hepatitis (INH) has been reported to have an incidence of 1 in 4,800 to 9,000 live births. Whereas biliary atresia ranges from 1 in 8,000 to 21,000 live births.⁹

Etiology

In United States (US), most commonly identifiable are biliary atresia (BA) (25%-35%), genetic disorders (25%), metabolic diseases (20%), and alfa-1 antitrypsin (A1AT) deficiency (10%).⁴ In Bangladesh, the cholestasis scenario is not different. Mahmud et al¹⁰ found BA in 37.4%, INH in 26.8%, Congenital infections in 24.9%, metabolic in 6.2%, choledochal cyst in 2.5% and ductal paucity in 2.5% cases.

History

Family history of consanguinity & miscarriage may reveal genetic disease while the obstetric history like fever with rash may reveal maternal infection (TORCH).¹¹ History of pre-term low birth weight (PLBW), intrauterine growth retardation (IUGR), small for gestational age may reveal to intrahepatic cholestasis (congenital infections) whereas term,

normal weight baby more in favor of biliary atresia.^{9,11} History of onset of jaundice is also crucial. Yachha et al¹² showed that the age of onset of jaundice in BA was 3-12 days and that of hepatocellular causes was 16-24 days. However, the mean age of presentation to a tertiary care center was 2.8-3.9 months compared to the desired age of evaluation is 4-6 weeks.¹²⁻¹⁴

Clinical Presentation

The most common findings of cholestasis are prolonged jaundice, acholic stools, dark yellow urine, and hepatomegaly. Jaundice may decrease over the first weeks of life as the indirect bilirubin decreases, thus giving a false impression that the jaundice is resolving.¹¹ On the other side, babies with BA appear well and have normal growth and development in spite of their jaundice, and this leads to parents and physicians underestimating the seriousness of the problem.⁴ The presence of acholic stools is suggestive, but not diagnostic of extra-hepatic biliary obstruction, since this can also be present in severe intrahepatic cholestasis. On the other hand, the presence of pigmented stools suggests patency of the extra-hepatic biliary tree and generally makes biliary atresia unlikely. However, in the early course of biliary atresia, stools may appear normally or intermittently pigmented and therefore, it is important that stool color be serially assessed.¹¹ It is well recognized that parents and health care professionals assess stool pigmentation subjectively and abnormally pale stools are frequently misinterpreted as normal.¹ Stool color charts may be helpful in review of history and ascertaining lack of pigmentation of stools in children with suspected liver disease. In Taiwan, use of a stool color card proved to be effective with 95.2% sensitivity for pale stools.^{15,16} A large prospective cohort study using

Correspondence to : Prof. Syed Shafi Ahmed, Professor and Head, Department of Pediatric Gastroenterology Hepatology and Nutrition, Bangladesh Institute of Child Health (BICH) and Director, Dhaka Shishu (Children) Hospital. Cell: 01711144371, E-mail: ahmedmuaz@yao.com

Received: 03 January 2019; **Accepted:** 05 May 2019

home-based screening for BA with a stool card proved cost effective in Canada.¹⁷ Physical examination of the cholestatic infant may reveal hepatomegaly or hepato-splenomegaly.⁹ Splenomegaly can be observed in about half of cases, particularly in infants who have infections, cirrhosis and portal hypertension. A palpable mass in the right upper quadrant may indicate a choledochal cyst. Dysmorphic facial features can suggest syndromic and chromosomal (downs, alagille etc.) disorders. Patients who have Alagille syndrome have congenital heart disease (pulmonary stenosis), dysmorphic facies (triangular face, broad forehead, deep-set eyes and small pointed chin), and butterfly vertebrae.² Posterior embryotoxon can be found in Alagille syndrome, chorioretinitis in cytomegalovirus infections and cataract in rubella or galactosemia. In an acutely ill infant sepsis, shock, heart failure, hypopituitarism, and metabolic disorders such as galactosemia or tyrosinemia should be evaluated promptly. Some infants show coagulopathy secondary to vitamin K malabsorption and deficiency, and present with bleeding (gastrointestinal blood loss, bleeding from the umbilical stump, intracranial hemorrhage). Coagulopathy may also be caused by liver failure, cirrhosis and severe liver disease (as in neonatal hemochromatosis).¹¹

Investigations

The most important initial investigation is the measurement of fractionated serum bilirubin levels. Infants who have cholestasis will have >1 mg/dL conjugated bilirubin when the total bilirubin is ≤ 5 mg/dL or >20 % of the total bilirubin level if total bilirubin is >5 mg/dL.^{2,11,18,19} Serum transaminases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are sensitive indicators of hepatocellular injury but are neither specific nor of prognostic value. Elevated levels of alkaline phosphatase can be found in biliary obstruction but also in the course of bone and kidney diseases. α -Glutamyltranspeptidase (GGT) is an enzyme in the biliary epithelium whose increase is strongly associated with cholestatic disorders like biliary atresia, choledochal cyst (extra-hepatic obstructions), as well as $\alpha 1$ -antitrypsin deficiency, Alagille syndrome and idiopathic neonatal hepatitis (intra-hepatic obstructions). However, a low or

normal GGT out of proportion to the degree of cholestasis suggests the presence of progressive familial intrahepatic cholestasis (PFIC) type 1, PFIC type 2 and an inborn error of bile acid synthesis.^{2,4,11}

Abdominal ultrasonography findings described in BA include the triangular cord sign (cone-shaped fibrotic mass cranial to the bifurcation of the portal vein), abnormal gallbladder morphology (not visualized or length <1.9 cm or lack of smooth/complete echogenic mucosal lining with an indistinct wall or irregular/lobular contour), no contraction of the gallbladder after oral feeding and non-visualized common bile duct (CBD).^{2,4} It is recommended that ultrasound should be done after 4 hours of fasting.² Ultrasound can also detect polysplenia or asplenia and choledochal cyst.² Hepatobiliary scintigraphy is carried out using Technetium-99 m-labeled hepatobiliary-immuno-di-acetic acid (HIDA) derivatives (Tc-99 IDA). The best resolution is achieved if the patient is administered a pre treatment with phenobarbitone (5 mg/kg/d) for at least 3 days previously. Slow uptake of the injected radioisotope or non-visualization of the liver with persistence of the cardiac pool suggests hepatocellular dysfunction, whereas non-visualization of the radioisotope in the small intestine from 4 to 24 hours suggests either bile duct obstruction or the severe inability of the hepatocyte to secrete.^{2,4,11} The sensitivity of scintigraphy for biliary atresia is relatively high (83 %-100 %); however, its specificity is low (33 %-80 %).^{20,21} In fact, since hepatobiliary scintigraphy is expensive, time consuming and poorly specific, many centers do not routinely use this test in the evaluation of cholestatic infants because it may delay the diagnostic evaluation without providing definitive diagnostic information.²²⁻²⁵ The diagnostic value of 3-dimensional MRCP for biliary atresia reported sensitivity 99% but specificity 36%.²⁶ Now a days, insufficient data are available for MRC evaluation of cholestatic infant and further studies are required to recommend routinely this modality.^{9,26,27}

Liver biopsy is the single most definitive investigation in the evaluation of neonatal cholestasis. In several single center studies, a diagnosis of biliary atresia was correctly suggested by liver biopsy histological findings in 90 to 95 % of cases and avoid unnecessary surgery in patients with intrahepatic disease.^{1,11,28-30} The diagnostic histologic appearances of biliary atresia include bile

duct proliferation, bile plugs in the portal tract bile duct, portal tract edema and fibrosis. Liver histology also useful for the diagnosis of other specific conditions, such as α 1-antitrypsin deficiency, some metabolic liver diseases, Alagille syndrome, neonatal sclerosing cholangitis, and viral infection (cytomegalovirus or herpes simplex).¹¹ Over liver biopsy, intra-operative cholangiogram (IOC) remains the gold standard for diagnosis of biliary atresia.^{1,4}

To establish a definite diagnosis, specific tests necessary. For congenital infections, TORCH screening with urinary CMV PCR, hormonal assay for hypothyroidism, non-glucose reducing substance (NGRS) with specific enzyme assay for galactosemia, urine or serum succinyl acetone for tyrosinemia, and serum ferritin for Hemochromatosis. Genetic testing may needed in progressive familial intra-hepatic cholestasis (PFIC), Alagille syndrome and galactosemia.^{1,4,11}

Management

Most infants with neonatal cholestasis are underweight and will need nutritional support. In breastfed infants, breastfeeding should be encouraged and medium-chain triglyceride (MCT) oil should be administered in a dose of 1-2 mL/Kg/d in 2-4 divided doses in expressed breast milk. In older infants, a milk-cereal-mix fortified with MCT is preferred. Fat soluble vitamins (Vitamin-A,D,E,K), water soluble vitamins, calcium, zinc and folic acid plays a major role to prevent malnutrition and malabsorption.^{1,2,4} Maintenance of bile flow along with management of pruritus much necessary. Ursodeoxycholic acid is the 1st line. Cholesteramine or phenobarbital may also added.^{4,9,11} It is crucial to rapidly identify infants who have medically treatable forms of cholestasis as well as those causes amenable to surgical intervention. Hepatoportoenterostomy (Kasai procedure) and surgical excision of choledochal cyst are the standard one. The rate of success in re-establishing bile flow is dependent on the age of the infant when the hepatic PE is performed as well as on the experience of the surgeon. There is up to an 80% success rate if the surgery takes place at less than 30 to 45 days of age. The success of surgery is shown by the excretion of bile and improvement of jaundice.¹¹ Anti-viral agents for congenital infections, hormone replacement for hypopituitarism, Galactose-free diet for galactosemia and low tyrosine diet for

tyrosinemia may advised. Iron chelation therapy and liver transplantation may needed in hemochromatosis.^{4,9,11}

Conclusion

NC constitutes almost one-third of children with chronic liver disease. Biliary atresia, neonatal hepatitis and metabolic causes are the most important etiology. Careful history, thorough physical examination, and fractionation of serum bilirubin are recommended in any infant with jaundice seen after 2 weeks of life. Late diagnosis of biliary atresia must be avoided because its surgical treatment is much more successful when performed before 30 to 45 days of life. The screening program with stool color card could be a useful tool for avoiding the late referral as well as improving the prognosis of patients with biliary atresia in the next future.

References

1. Fawaz R, Baumann U, Ekong U, Fischler B, Hadzic N, Mack CL, et al. Guideline for the evaluation of cholestatic jaundice in infants: Joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology & Nutrition and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2017;**64**:154-68.
2. Feldman AG, Sokol RJ. Neonatal Cholestasis. *Neoreviews* 2013;**14**:e63-e71.
3. Venigalla S, Gourley GR. Neonatal cholestasis. *Semin Perinatol* 2004;**28**:348-55.
4. Bhatia V, Bavdekar A, Mathai J, Waikar Y, Sibal A. Management of neonatal cholestasis: Consensus statement of the pediatric gastroenterology chapter of Indian Academy of Pediatrics. *Indian Pediatr* 2014; **51**:203-10.
5. Consensus report on neonatal cholestasis syndrome. Pediatric Gastroenterology Subspecialty Chapter of Indian Academy of Pediatrics. *Indian Pediatr* 2000;**37**:845-51.
6. Yachha SK, Khanduri A, Kumar M, Sikora SS, Saxena R, Gupta RK, et al. Neonatal cholestasis syndrome: an appraisal at a tertiary center. *Indian Pediatr* 1996;**33**:729-34.
7. Arora NK, Arora S, Ahuja A, Mathur P, Maheshwari M, Das MK, et al. Alpha 1 antitrypsin deficiency in children with chronic liver disease in North India. *Indian Pediatr* 2010;**47**:1015-23.

8. Yachha SK, Sharma BC, Khanduri A, Srivastava A. Current spectrum of hepatobiliary disorders in northern India. *Indian Pediatr* 1997;**34**:885-90.
9. Suchy FJ. Neonatal Cholestasis. *Pediatr Rev* 2004; **25**:388-96.
10. Mahmud S, Ahmed SS, Parvez M, Tasneem F, Afroz M. Etiology of Neonatal Cholestasis: An experience in a Tertiary Centre of Bangladesh. *DS (Child) H J* 2016;**32**:22-26.
11. Dani C, Pratesi S, Raimondi F, Romagnoli C. Italian guidelines for the management and treatment of neonatal cholestasis. *Italian J Pediatrics* 2015;**41**: 1-12.
12. Yachha SK, Sharma A. Neonatal cholestasis in India. *Indian Pediatr* 2005;**42**:491-92.
13. Yachha SK. Cholestatic jaundice during infancy. *Indian J Gastroenterol* 2005;**24**:47-48.
14. Poddar U, Thapa BR, Das A, Bhattacharya A, Rao KL, Singh K. Neonatal cholestasis: differentiation of biliary atresia from neonatal hepatitis in a developing country. *Acta Paediatr* 2009;**98**:1260-64.
15. Bakshi B, Sutcliffe A, Akindolie M, et al. How reliably can paediatric professionals identify pale stool from cholestatic newborns? *Arch Dis Child Fetal Neonatal Ed* 2012;**97**:F385-F387.
16. Chen SM, Chang MH, Du JC. Screening for biliary atresia by infant stool color card in Taiwan. *Pediatrics* 2006;**117**:1147-54.
17. Schreiber RA, Masucci L, Kaczorowski J, et al. Home-based screening for biliary atresia using infant stool colour cards: a large-scale prospective cohort study and cost-effectiveness analysis. *J Med Screen* 2014; **21**:126-32.
18. Harpavat S, Finegold MJ, Karpen SJ. Patients with biliary atresia have elevated direct/conjugated bilirubin levels shortly after birth. *Pediatrics* 2011;**128**:e1428-e1433.
19. Davis AR, Rosenthal P, Escobar GJ, Newman TB. Interpreting conjugated bilirubin levels in newborns. *J Pediatr* 2011;**158**:562.
20. Gilmour SM, Hershkop M, Reifen R, Gilday D, Roberts EA. Outcome of hepatobiliary scanning in neonatal hepatitis syndrome. *J Nucl Med* 1997; **38**:1279-82.
21. Esmaili J, Izadyar S, Karegar I, Gholamrezanezhad A. Biliary atresia in infants with prolonged-cholestatic jaundice: diagnostic accuracy of hepatobiliary scintigraphy. *Abdom Imaging* 2007; **32**:243-47.
22. Kianifar HR, Tehranian S, Shojaei P, Adinehpour Z, Sadeghi R, Kakhki VR, et al. Accuracy of hepatobiliary scintigraphy for differentiation of neonatal hepatitis from biliary atresia: systematic review and meta-analysis of the literature. *Pediatr Radiol* 2013;**43**:905-19.
23. Moyer V, Freese DK, Whittington PF, Olson AD, Brewer F, Colletti RB, et al. Guideline for the evaluation of cholestatic jaundice in infants: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2004;**39**: 115-28.
24. Yang JG, Ma DQ, Peng Y, Song L, Li CL. Comparison of different diagnostic methods for differentiating biliary atresia from idiopathic neonatal hepatitis. *Clin Imaging* 2009;**33**:439-46.
25. Sevilla A, Howman-Giles R, Saleh H, Trpezanovski J, Concannon R, Williams K, et al. Hepatobiliary scintigraphy with SPECT in infancy. *Clin Nucl Med* 2007;**32**:16-23.
26. Norton KI, Glass RB, Kogan D, Lee JS, Emre S, Shneider BL. MR cholangiography in the evaluation of neonatal cholestasis: initial results. *Radiology* 2002;**222**:687-91.
27. Liu B, Cai J, Xu Y. Three-dimensional magnetic resonance cholangiopancreatography for the diagnosis of biliary atresia in infants and neonates. *PLoS One* 2014;**9**:e88268.
28. Lee WS, Looi LM. Usefulness of a scoring system in the interpretation of histology in neonatal cholestasis. *World J Gastroenterol* 2009;**15**:5326-33.
29. Zerbini MC, Gallucci SD, Maezono R, Ueno CM, Porta G, Maksoud JG, et al. Liver biopsy in neonatal cholestasis: a review on statistical grounds. *Mod Pathol* 1997;**10**:793-99.
30. Rastogi A, Krishnani N, Yachha SK, Khanna V, Poddar U, Lal R. Histopathological features and accuracy for diagnosing biliary atresia by prelaparotomy liver biopsy in developing countries. *J Gastroenterol Hepatol* 2009;**24**:97-102.