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Original Article

# Etiologies of neonatal cholestasis at a tertiary hospital in Bangladesh

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## Abstract

***Background*** Neonatal cholestasis is an important etiology of chronic liver disease in young children. It has a varied etiology. There is considerable delay in presentation and diagnosis of neonatal cholestasis in Bangladesh. Lack of awareness and knowledge among the pediatricians regarding etiological diagnosis and outcome of neonatal cholestasis is the reasons for poor outcome in major portion of cases in Bangladesh.

***Objective*** To evaluate the etiological spectrum of neonatal cholestasis.

***Methods*** This retrospective study was conducted at the Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. We reviewed medical records of children who were diagnosed with neonatal cholestasis. Complete diagnostic profiles of every cases with age of presentation, male-female ratio and final diagnosis were analyzed.

***Results*** A total of 114 children with neonatal cholestasis were evaluated. Subjects' male-female ratio was 1.92: 1.0, and mean age at hospitalization was 92.7 (SD 39.5) days. Biliary atresia was the most common etiology (47.4%), followed by idiopathic neonatal hepatitis/INH (21.9%). Other identified etiologies were, toxoplasmosis, others (syphilis, varicella-zoster, parvovirus b19), rubella, cytomegalovirus (CMV), and herpes/TORCH infection (8.61%), progressive familial intrahepatic cholestasis/PFIC (4.4%), galactosemia (4.4%), choledochal cyst (3.5%), sepsis (1.8%), urinary tract infection/UTI (1.8%), hypothyroidism (1.8%), lipid storage disease/Niemann-Pick disease (0.9%), non-syndromic paucity of interlobular bile ducts (2.67%), and Caroli's disease (0.9%).

***Conclusion*** In Bangladesh, neonatal cholestasis cases are most often due to obstructive causes, particularly biliary atresia. Idiopathic (INH), infectious (primarily TORCH), metabolic, and endocrine causes followed in terms of frequency. **[Paediatr Indones. 2020;60:66-70; doi: http://dx.doi.org/10.14238/pi60.2.2020.66-70** ].

***Keywords:*** *neonatal cholestasis; biliary atresia; idiopathic neonatal hepatitis*

Neonatal cholestasis is defined as conjugated hyperbilirubinemia occurring in newborns within the first three months of life, due to a group of hepatobiliary disorders.[1,2] Jaundice is due to increased serum bilirubin concentration and becomes apparent in infants when the serum bilirubin level reaches >4 to 5 mg/dL.[3,4] Jaundice in the first 2 weeks of life is common, occurring in 2.4-15% of newborns.[5] Most often, this jaundice is due to unconjugated hyperbilirubinemia and resolves spontaneously,[6] but cholestatic jaundice in infancy is an uncommon and potentially serious problem that indicates hepatobiliary dysfunction.[6]

Conjugated hyperbilirubinemia in a neonate is defined as a serum direct/conjugated bilirubin concentration >1 mg/dL if the total serum bilirubin

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(TSB) is <5 mg/dL, or >20% of TSB if the TSB is ≥5 mg/dL.[7] The incidence of neonatal cholestasis is 1 in 2,500-5,000 live births.[6] Early and accurate diagnosis of neonatal cholestasis is crucial for proper management because some causes are treatable.[8] In the past, idiopathic neonatal hepatitis (INH) was the most common diagnosis, with an incidence of 1 in 4,800 to 1 in 9,000 live births.[9,10] Currently, the most commonly identifiable cause of neonatal cholestasis is biliary atresia (BA), accounting for 20-35% of neonatal cholestasis cases.[11,12] Genetic disorders and metabolic disease are also common etiologies. Congenital toxoplasmosis, rubella, cytomegalovirus, and herpes simplex (the TORCH infections) account for about 5% of cases. Differential diagnoses include obstructive conditions (biliary atresia, choledochal cyst, syndromic and non-syndromic paucity of interlobular bile ducts, inspissated bile syndrome, Caroli's disease), genetic conditions (alpha-1-antitrypsin deficiency, Alagille syndrome, progressive familial intrahepatic cholestasis/PFIC, cystic fibrosis), infectious disease (congenital TORCH infection, bacterial sepsis, urinary tract infection), metabolic conditions (bile acid synthesis defects, gestational alloimmune liver disease/neonatal hemochromatosis, galactosemia, hereditary tyrosinemia, storage diseases), and endocrine conditions (hypothyroidism, panhypopituitarism), histiocytosis, parenteral nutrition, as well as drugs.[6]

The aim of the study was to evaluate the etiological spectrum of neonatal cholestasis.

## Methods

This retrospective, observational study was carried out in the Department of Pediatric Gastroenterology, BSMMU, Dhaka, Bangladesh. We reviewed the departmental register book (inpatients) from January 2017 to December 2018. Children diagnosed with neonatal cholestasis were included in this study. Diagnostic evaluations included complete blood count, liver function tests, urine for non-glucose reducing substances, urine cultures, TORCH screening, ultrasonography of the hepatobiliary system (fasting and after feeding), thyroid function tests, hepatobiliary scintigraphy, and liver biopsies. Eye evaluation was done for cataracts, chorioretinitis, cherry red spots, posterior embryotoxon, and hypoplasia of the optic discs. Patients with incomplete data were excluded from this study. A total of 114 patients were evaluated and data were entered into Microsoft Excel and analyzed by *SPSS s*oftware. This study got ethical approval from Departemental Review Board (DRB) of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka.

## Results

A total of 114 children with neonatal cholestasis were included, 65.8% males and 34.2% females, with a 1.92:1 male: female ratio. Mean age at hospitalization was 92.7 (SD 39.5) days ranging from 23 to 270 days of age.

In the study population, an obstructive cause was most common (58.9%), followed by idiopathic (21.9%), infectious (12.2%), metabolic (5.3%), and endocrine (1.8%) causes. In terms of etiologic diagnoses, biliary atresia was most common (47.4%) followed by INH (21.9%), TORCH infection (8.6%), PFIC (4.4%), galactosemia (4.4%), choledochal cyst (3.5%), sepsis (1.8%), UTI (1.8%), hypothyroidism (1.8%), lipid storage disease/Niemann-Pick disease (0.9%), non-syndromic paucity of interlobular bile ducts (2.7%), and Caroli's disease (0.9%) (**Table 1**).

**Table 1**. Etiological profiles of neonatal cholestasis

| Etiologi | (N=114) |
|---|---|
| Obstructive causes, n (%) | |
| Biliary atresia | 48 (42.1) |
| Biliary atresia with CMV | 5 (4.4) |
| Biliary atresia with HSV | 1 (0.9) |
| Non-syndromic paucity of interlobular bile ducts | 3 (2.7) |
| Choledochal cyst | 4 (3.5) |
| Caroli's disease | 1 (0.9) |
| PFIC | 5 (4.4) |
| INH | 25 (21.9) |
| Infectious cause, n (%) | 7 (6) |
| CMV | 1 (0.9) |
| Toxoplasma | 1 (0.9) |
| CMV+HSV | 1(0.9) |
| Sepsis | 2 (1.8) |
| UTI | 2 (1.8) |
| Metabolic causes, n (%) | |
| Galactosemia | 5 (4.4) |
| Niemann-Pick disease | 1 (0.9) |
| Endocrine cause, n (%) | |
| Hypothyroidism | 2 (1.8) |

CMV=cytomegalovirus, HSV= herpes simplex virus

## Discussion

Early and accurate diagnosis is essential for good neonatal cholestasis outcomes. Prognosis of biliary atresia is dependent on the timing of operative management, as delayed diagnosis worsens the outcome.[13] In our study, the mean age at hospitalization was 92.7 (SD 39.5, range 23-270) days and the male: female ratio was 1.92: 1. Similarly, a previous study found that mean age at presentation was 105 95 days.[4] Jain et al. reported that median age at presentation was 78 (range 15-270) days and male: female ratio was 1.17: 1,14 while a study reported that mean age at presentation was 58.3 (SD 15.3, range 1-120) days and male: female ratio was 1.63:1.[15] Physicians at primary health centers in Bangladesh have little knowledge of neonatal cholestasis, so patients tend to be referred at a significant delay. Parents also prefer to consult traditional healers before coming to the tertiary centers. Furthermore, laboratory investigation facilities are not available at every center. All these factors are responsible for delayed presentation and diagnosis.

A wide variety of etiologies are responsible for neonatal cholestasis. These are broadly categorized as obstructive, metabolic, genetic, infectious, endocrine and malignant causes, as well as parenteral nutrition, and drugs.[6] We found that an obstructive cause was most common (58.81%), followed by idiopathic causes (21.9%). As full investigation facilities are not available in Bangladesh, INH contributed a sizeable portion of neonatal cholestasis in our study, as other possiblilties could not be identified. Other causes included infectious (12.21%), metabolic (5.27%), and endocrine (1.8%) causes. Most mothers and caregivers in rural areas have poor knowledge about hygiene in caring for neonates, thus infants are predisposed to neonatal sepsis. In addition, consanguinity is very common in Bangladesh, so metabolic diseases are not uncommon as an etiology of neonatal cholestasis. A consensus report on neonatal cholestasis syndrome by the *Indian Academy of Pediatrics* stated that obstructive causes were most common (41%), followed by idiopathic (30%), infectious (17%), metabolic (4%), and other (8%) causes.[16] In addition, a previous study found that obstructive causes were most common (36%), followed by idiopathic (31%), infectious (18%), metabolic (12%), and other (5.2%) causes.[17] Other studies had similar findings.[14,18-20] However, Karim *et al.*[4] found that obstructive and idiopathic causes were nearly equal, and infective causes were most common. Another study found idiopathic causes in 25%, metabolic/genetic causes in 23%, biliary obstruction in 20%, parenteral nutrition in 20%, infection in 9%, and bile duct hypoplasia in 3%.[21]

Regarding specific etiologic diagnoses, we found that biliary atresia was most common (47.37%), followed by INH (21.9%), TORCH infection (8.61%), PFIC (4.4%), galactosemia (4.4%), choledochal cyst (3.5%), sepsis (1.8%), UTI (1.8%), hypothyroidism (1.8%), lipid storage disease -Niemann-Pick disease (0.87%), non-syndromic paucity of interlobular bile ducts (2.67%), and Caroli's disease (0.87%). A previous study found that neonatal cholestasis patients had biliary atresia (25.8%), INH (24.2%), TORCH infection (28.3%), urinary infection (7.2%), choledochal cyst (6.5%), hypothyroidism with CMV infection (1.6%), Down syndrome with hypothyroidism (1.6%), Crouzon syndrome with hypothyroidism (1.6%), and alpha-1 antitrypsin deficiency (1.6%).[4] A previous study noted INH in 26.0% of cases, extrahepatic biliary atresia in 25.89 %, infection in 11.47 %, TPN-associated cholestasis in 6.44 %, metabolic disease in 4.37 %, alpha-1 anti-trypsin deficiency in 4.14 %, and perinatal hypoxia/ischemia in 3.66 %. Cytomegalovirus was the most common infection identified (31.51%) and galactosemia (36.49%) was the most common metabolic disease identified.[22] In our study, we also found CMV to be the most common infection and galactosemia to be the most common metabolic etiology. See **Table 2** for a summary of etiologies from eight neonatal cholestasis studies.

In conclusion, neonatal cholestasis has a varied etiology. Delayed diagnosis may be due to late presentation at specialized centers. Obstructive causes (primarily biliary atresia) are most common, followed by idiopathic (INH), infectious, metabolic, and endocrine causes.

**Table 2**. Etiologies of neonatal cholestasis in different studies

| Study | Location | No. of patients | BA (%) | INH (%) | Metabolic (%) | Intrahepatic ductal paucity (%) | Infectious (%) | Others (%) |
|---|---|---|---|---|---|---|---|---|
| Present study | Bangladesh | 114 | 47.4 | 21.9 | 5.3 | 2.7 | 12.2 | 10.6 |
| Karim B *et al.*, 2005 | Bangladesh | 62 | 25.8 | 24.2 | 1.6 | 3.2 | 35.5 | 8.3 |
| Yachha SK, 2005 | India | 60 | 55 | 23 | 3 | 11 | | |
| Arora NK *et al.*, 2010 | India | 420 | 30 | 31 | 12 | 1 | 18 | 4.2 |
| Consensus report on neonatal cholestasis syndrome, IAP | India | 1008 | 34 | 30 | 4 | 3 | 17 | 12 |
| Mieli-Vergani G *et al.*, 1989 | England | 50 | 34.7 | 30.5 | 17.4 | 5.6 | 8.7 | 3.1 |
| Jain M *et al.*, 2016 | India | 100 | 41 | 18 | | | 34 | 7.7 |
| Mahmud S *et al.*, 2016 | Bangladesh | 80 | 37.5 | 25 | 3.3 | 5 | 25.3 | 3.9 |

## Conflict of Interest

None declared.

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