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ORIGINAL ARTICLE

Etiology of Neonatal Cholestasis: An Experience in a Tertiary Centre of Bangladesh

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Abstract

Background*: Neonatal cholestasis is a major cause of morbidity & mortality in young infants. It has a varied etiology and difficult diagnostic problem. The disorder has rarely been studied in centers from Bangladesh.*

Objective: *To determine the etiology of both extra-hepatic & intra-hepatic cholestasis at a tertiary referral center in Bangladesh.*

Materials & Methods: *A prospective, descriptive study was done in the department of Pediatric Gastroenterology, Hepatology & Nutrition, Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh from January 2014 to June 2016 among 80 infants who presented with cholestatic jaundice in <1 year of age.*

Results: *Out of 80 children, 48 (60%) were intra-hepatic causes & 32 (40%) were extra-hepatic causes. Among all cholestasis, biliary atresia (BA) 30 (37.5%), idiopathic neonatal hepatitis (INH) 20 (25%) and TORCH infections 19 (23.7%) were the commonest ones. Among 32 extra-hepatic cholestasis, predominant causes were biliary atresia 30 (93.7%) followed by choledochal cyst 2 (5.3%). In 48 Intra-hepatic cholestasis, idiopathic neonatal hepatitis (INH) 20 (41.6%) and TORCH infections 19 (39.5%) were the dominant ones. Two (4.1%) cases of hypothyroidism, galactosemia and intra-hepatic bile duct paucity (non-syndromic) each. Down's syndrome with hypothyroidism, urinary tract infection (UTI) with sepsis and progressive familial intra-hepatic cholestasis (PFIC) were evaluated in 1 (2%) case of each. Among 19 TORCH infections, Cytomegalovirus (CMV) 13 (68.4%) was the commonest followed by CMV with herpes-simplex virus (HSV) co-infection 4 (21.1%) and Toxoplasmosis 2 (10.5%).*

Conclusion: *The more frequent etiological factors were biliary atresia (BA), idiopathic neonatal hepatitis (INH) & TORCH infections. CMV were predominant cause of TORCH infections.*

Key words: *Neonatal cholestasis, cholestatic jaundice, biliary atresia, Idiopathic neonatal hepatitis, Conjugated hyperbilirubinemia.*

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Introduction

Cholestatic jaundice in infancy is an uncommon but potentially serious problem that indicates hepatobiliary dysfunction. [1] Neonatal cholestasis 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 d"5 mg/dl, or >20% of total serum bilirubin when it is >5 mg/dl. [2,3] Conjugated hyperbilirubinemia at any age in a newborn is pathological and requires evaluation. Any new born with jaundice and dark yellow urine staining the diaper with or without pale stools should be strongly suspected to have neonatal cholestasis.[4]

Idiopathic neonatal hepatitis (INH) and biliary atresia are the most frequent causes of cholestatic jaundice in the first months of life.[5,6] Syndrome of neonatal hepatitis has diverse causes. Idiopathic form, sepsis/ urinary tract infection, genetic diseases of metabolism and congenital infections are relatively common causes compared to toxic causes, post-haemolytic states, neonatal acute hepatic necrosis, parenteral nutrition, chromosomal anomalies, familial syndromes etc.[7]

The aim of this prospective, descriptive study is to determine common etiological factors of cholestasis in infants attending a tertiary care hospital of Bangladesh.

Materials and methods

A prospective, descriptive study was conducted in the department of Pediatric Gastroenterology, Hepatology & Nutrition, Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh from January 2014 to June 2016. A total of 80 admitted cases of neonatal cholestasis defined by conjugated bilirubin is higher than 1 mg/dl, if the total serum bilirubin is d"5 mg/dl, or >20% of total serum bilirubin when it is >5 mg/dl, age <1 year, both sexes were enrolled in this study. Patients e"1 year, jaundice due to other causes were excluded from the study.

Complete blood count with culture and liver function tests (S. bilirubin total, direct, indirect, Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), Gamma-glutamyl transpeptidase, (GGT) Prothrombine time (PT) and albumin were done. Urine was tested for non-glucose reducing substances (NGRS) and for bacterial culture. Ultrasonography of hepatobiliary system (fasting & after feed) was done in all cases. Hepatobiliary scintigraphy (HIDA scan) was done from Institute of Nuclear Medicine, Bangabandhu Sheikh Mujib Medical University after administration of phenobarbitone (5 mg/kg/day orally in two divided doses for at least 5 days). At scintigraphy, absence of radioactivity in the small bowel after 24 hours was taken as absent tracer excretion. The biopsy was done with the help of Automated Biopsy Gun (18G×16 cm, PD 22 mm) under local anesthetics (2% lidocaine) and intravenous midazolam (0.1 mg/kg) with 3 hours fasting. The biopsy specimens were immediately fixed in 10% formal-saline. Biopsy was not done in patients with huge ascites, Hemoglobin <10 gm/dl, platelet count <80,000/cu mm, increased prothrombin time (INR >1.3), prolong bleeding and/or clotting time and lack of parental consent.

Biliary atresia were diagnosed on the basis of clinical (full term with good birth weight and persistent pale stool), biochemical (moderate elevation of serum bilirubin, ALT but high elevation of ALP & GGT), ultrasonographic (non-visualized/contracted/small gall bladder), scintigraphc (absent tracer excretion) and liver biopsy (bile ductular proliferation, portal tract fibrosis & bile plugs in portal triads).

To identify the intra-hepatic causes of cholestasis, TORCH screening, thyroid function test and HBsAg were done. If Cytomegalovirus (CMV) IgM positive or IgG >10 fold than normal then urinary CMV PCR was done. Katyotyping was done in one suspected case of Down's syndrome and Galactose-1-phosphate uridylyltransferase (GALT) assay only in NGRS positive cases. Intra-hepatic bile duct paucity was diagnosed by characteristic biopsy finding and PFIC (Type I/II) was diagnosed by low or normal GGT as DNA testing not available here. When all test results were insignificant for any condition, then termed as idiopathic neonatal hepatitis.

A preformed semi structured data collecting form was used as a data collection instrument. Data were collected by the researcher and analyzed by Statistical Package of Social Science (SPSS) version 11.5 programme.

Results

All the children were <1 year of age. Out of 80 children, 48 (60%) were intra-hepatic cholestasis & 32 (40%) were extra-hepatic cholestasis (Fig-1).

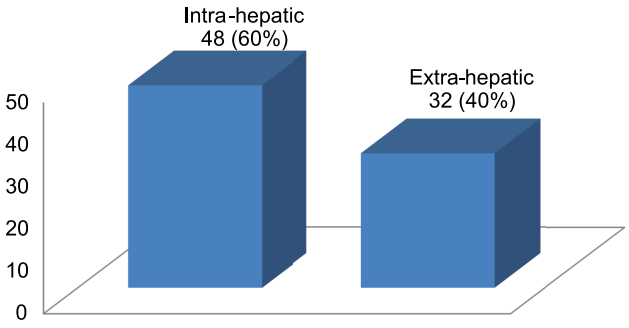

Fig 1 *Incidence of Intra-hepatic & Extra-hepatic cholestasis*

Among all children, biliary atresia (BA) 30 (37.5%) were the cause of cholestasis for most of the cases followed by idiopathic neonatal hepatitis (INH) 20 (25%) and TORCH infections 19 (23.7%) (Fig-2).

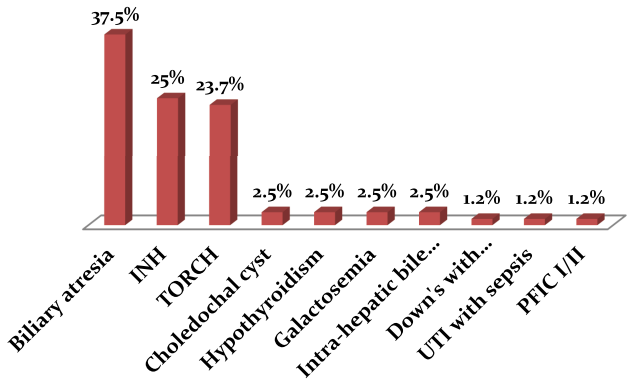

Fig 2 *Etiology of neonatal cholestasis*

Among 32 extra-hepatic cholestasis, biliary atresia (BA) 30 (93.7%) were the most common cause followed by choledochal cyst 2 (6.3%) (Fig-3).

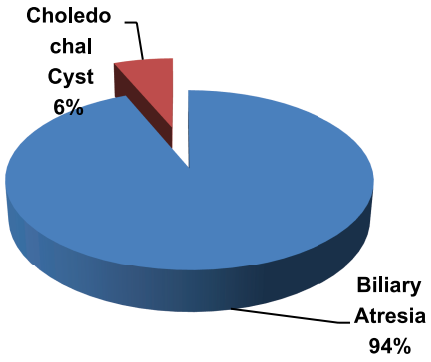

Fig 3 *Causes of Extra-hepatic cholestasis*

Among 48 intra-hepatic cholestasis, most common were idiopathic neonatal hepatitis 20 (41.6%) & TORCH infections 19 (39.5%). Among others, hypothyroidism, galactosemia and intra-hepatic bile duct paucity were found in 2 (4.1%) cases of each. Down's syndrome with hypothyroidism, UTI with sepsis and PFIC were found in 1 (2.0%) case of each (Fig-4)

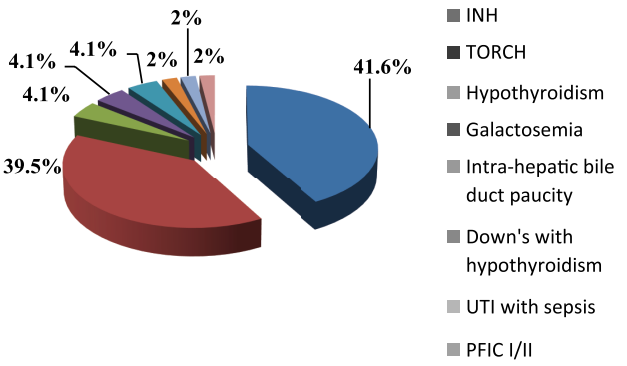

Fig 4 *Causes of Intra-hepatic cholestasis*

Among 19 TORCH infections, Cytomegalovirus (CMV) 13 (68.4%) were the most commonest followed by CMV with herpes-simplex virus (HSV) co-infection 4 (21.1%) and Toxoplasmosis 2 (10.5%) (Fig-5).

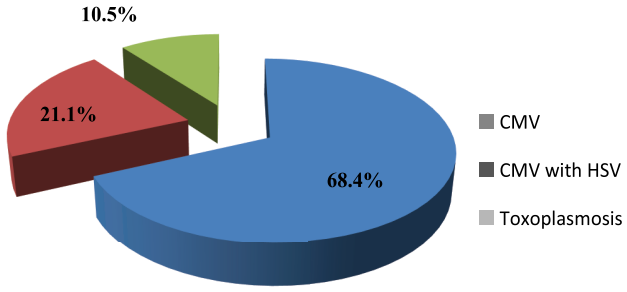

Fig 5 *Responsible viruses in TORCH infection*

Discussion

Diagnosis of cholestatic disorder is difficult because of lack of specificity of available diagnostic tests. On the other hand, early diagnosis & referral to the experienced centers is very important for proper management.[8] Many causes have been identified to cause injury to the newborn liver. These may include intrahepatic causes, which may be either sporadic or familial, and extrahepatic causes.[9]

In the present study from 80 infants, biliary atresia (BA) 30 (37.5%) were the most common cause of

neonatal cholestasis (NCS) followed by idiopathic neonatal hepatitis (INH) 20 (25%) & TORCH infections 19 (23.7%). Nahid et al[10] [BA-19 (31.6%), INH-19 (31.6%) & TORCH 13 (21.6%)], Karim et al[8] [(BA 19 (26.6%), INH 15 (24.2%) & TORCH 17 (27.4%)] from Bangladesh and Jain et al[11] [BA 41 (41%), INH-18 (18%) & neonatal hepatitis 20 (20%)] from India had similar findings. However, Hamid et al[12] were observed a different result where Neonatal hepatitis 18 (60%) were the most common followed by BA 12 (40%).

Among 32 cases of Extra-hepatic cholestasis, most of the infants suffering from BA 30 (93.7%) followed by choledochal cyst (CC) 2 (6.3%). From the desk of extra-hepatic cholestasis, Nahid et al.[10] [(BA 19 (90.5%) & CC 2 (9.5%)] also stated the similar result. BA is characterised by progressive fibrosing obliteration of both intra-hepatic and extrahepatic bile ducts. It is the most important cause of neonatal cholestasis worldwide, including Malaysia. It is also the most important indication for childhood liver transplantation the world over.[9]

Among 48 cases of Intra-hepatic cholestasis, INH 20 (41.6%) was the most frequent followed by TORCH infection 19 (39.5%). From 39 cases of intra-hepatic cholestasis, Nahid et al.[10] were observed INH 19 (48.7%) and TORCH infections 13 (33.3%). It has an incidence of 1:5000 births and constitutes approximately 50% of prolong neonatal jaundice.[13] Most patients in whom no aetiology was found were considered to have INH/transient neonatal cholestasis (TNC) by some authors. TNC was characterized by early-onset cholestasis, absence of a known cause of neonatal cholestasis, normalization of clinical and biochemical parameters during follow up and no history of some neonatal injurious events such as asphyxia, sepsis, total parenteral nutrition. As this study also had shown INH/TNC as one of the major reasons for cholestasis in infants.[7]

In 19 cases of TORCH infections, Cytomegalovirus (CMV) 13 (68.4%) were the commonest followed by CMV with herpes-simplex virus (HSV) co-infection 4 (21.1%) and Toxoplasmosis 2 (10.5%). Nahid et al[10]. [CMV 9 (69.2%, HSV 1 (7.1%), Toxoplasmosis 2 (14.2%)] and Hamid et al.[12] [(CMV 17 (73.9%, HSV 6 (26.1%)] of this country were stated the near similar result. A study in Srilanka, out of eight cases of intra-hepatic cholestasis 5 (62.5%) of them became positive for CMV infection.[7] Chang et al[13] also reported that most of their patients with neonatal hepatitis were due to CMV infection. It is important to have a well-organized and structured approach to detect TORCH related cholestasis, in particular CMV hepatitis. Because these were under.[7]

There are some endocrine, metabolic & genetic disorders may present with intra-hepatic cholestasis[13]. In our study among 48 cases of intra-hepatic cholestasis, isolated hypothyroidism in 2 (4.1%) and hypothyroidism with Down's syndrome in 1 (2%) case. Nahid et al.[10] were reported the near similar results among 39 intra-hepatic cases. Isolated hypothyroidism in 4 (10.2%) and hypothyroidism with Down's syndrome in 1 (2.5%) case. In another study on Bangladesh, Karim et al[8]. also observed hypothyroidism with down's syndrome and hypothyroidism with CMV infection in each 1 (2.3%) of cholestatic infant. In the present study, 2 (4.1%) cases of galactosemia among intra-hepatic cholestasis were diagnosed which were unlike in Nahid et al[10]. & Karim et al.[8] observation. This may due to using recent investigational approach like enzyme assay. Two (4.1%) cases of Intra-hepatic bile duct paucity (non-syndromic) were evaluated in the present study which were also evident in Karim et al.[8] [1 (1.6%)] observation. Luthufdeen et al[7]. were stated 2 (4.7%) infants of Alagille syndrome which was unlike our study. It may due to lack of genetic testing facility of our country. One (2%) case of Progressive Familial Intra-hepatic Cholestasis (PFIC) was diagnosed in our study which was like Nahid et al.[10] 1 (2.5%) study. Karim et al[8]. were reported 5 (11.9%) cases among 42 cases of neonatal cholestasis due to urinary tract infection (UTI) but we observed only 1 (2%) case of UTI with sepsis. It may due to increase awareness of parents as well as primary health care workers regarding early diagnosis and antibiotic use of any kind of infection. Tiker et al.[14] were reported that important cause of neonatal cholestasis was perinatal hypoxic-ischemia. Other studies have also identified the same factor of transient neonatal cholestasis. Bile secretion processes, which are already underdeveloped in neonates, can be further impaired by hepatic hypoxia-ischemia. No infants in our study having cholestasis with hypoxic-ischemic insult.

Limitations of study

The main limitation of the present study is that was a single-centre study with a limited sample size.

Conclusions

Biliary atresia, idiopathic neonatal hepatitis and TORCH infections were the commonest causes of neonatal cholestasis. Among extra-hepatic cholestasis biliary atresia and intra-hepatic cholestasis INH & TORCH infections were the commonest. In TORCH infections, CMV were the prominent one.

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