Original Article

Clinical Spectrum and Etiology of Neonatal Cholestasis: Experience in a tertiary care hospital of Bangladesh.

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Abstract:

Background: Misdiagnosis of neonatal cholestastatic jaundice as physiological jaundice delays the identification of important liver diseases.

Objectives: Aim of this study was to observe the clinical spectrum and etiologies of neonatal cholestasis.

Methods: This cross-sectional study was conducted at the department of Pediatric Gastroenterology and Nutrition of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from August 2013 through July 2015 among purposively sampled infants with neonatal cholestasis. For all patients, serum bilirubin total, direct and liver function tests were checked. Investigations were done for diagnosis of cause. Hepatobiliary scintigraphy and liver biopsy was done in all except those where diagnosis was otherwise confirmed.

Results: Total 124 neonatal cholestasis cases were studied and most of them 95(76.6%) were male. The mean age at admission was 83.6±40.3 days and mean age at onset of jaundice was 6.75±7.3days. The most common causes of neonatal cholestasis were idiopathic neonatal hepatitis (48, 38.7%), BA (38, 30.6%), congenital cytomegalovirus hepatitis (15,12.1%) and Hypothyroidism (7,5.6%) respectively. Common clinical features at presentation were jaundice (100%), pale colored stools (100%), hepatomegaly (100%) and splenomegaly (38.4%) respectively. Term baby, good birth weight and persistent pale colored stool were significantly higher in BA cases.

Conclusion: Among studied subjects Biliary atresia was found to be the most common identifiable cause of neonatal cholestasis. No single clinical feature was found to be significant for differentiating the causes. Jaundice with pale coloured stool and hepatomegaly was found to be the most common presenting clinical features of neonatal cholestasis.

Keywords: Neonatal Cholestasis, Biliary atresia, Idiopathic neonatal hepatitis, Etiology.

Introduction:

Neonatal cholestasis is a group of hepatobiliary disorders occurring within the first three months of life and is characterized by direct bilirubin value greater than 1.0 mg/dl, if the total bilirubin is less than 5 mg/dl or direct bilirubin of more than 20% of the total, if the total bilirubin is greater than 5 mg/dl.[1] About 15% of breast fed infants experience jaundice lasting for more than three weeks.[2] Neonatal cholestasis occurs in 0.04% to 0.2% of live births.[3] Biliary atresia (BA) and idiopathic neonatal hepatitis are the two most common etiologies of neonatal cholestatic jaundice.[4] Children with biliary atresia referred for surgery before 60 days of age do better than those older than 90 days.[5] Aim of this study was to observe the clinical spectrum and etiologies of neonatal cholestasis.

Material & Methods:

This cross sectional study was conducted on infants having neonatal cholestasis attending the Pediatric Gastroenterology and Nutrition department of BSMMU from August 2013 through July 2015. The clinical details including perinatal history were recorded and physical examination of all cases were done. For all patients, serum bilirubin total and direct, serum Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Gamma glutamyl transpeptidase (GGT) and Prothrombin time (PT) were checked. Investigations were done for diagnosis of

cause like infectious, metabolic and others. Abdominal ultrasonography (USG) was done after 4 h of fasting and repeated ½ hour after a feed. Hepatobiliary scintigraphy and liver biopsy were done in all except those where diagnosis was otherwise obvious or improving. After ensuring normal coagulation parameters, platelet count and informed written consent, percutaneous liver biopsy was done. For the purpose of comparison, all cases were grouped according to causes one group Biliary atresia (BA) and another group other causes of neonatal cholestasis (NC). The study was approved by the institute's ethical committee. Statistical analyses were carried out using the SPSS® statistical package, version 17 (SPSS Inc., Chicago, IL, USA) for Windows XP. Results were expressed as mean, standard deviation, range and frequency.

Results:

Initially a total 165 consecutive cases were selected as cases of neonatal cholestasis and after further diagnostic evaluations 41 cases were excluded. Among the excluded subjects 6 were severely ill and in 35 cases full diagnostic evaluation and liver biopsy could not be done. One twenty four patients were selected as study subjects. The underlying etiologies of NC of the studied patients are shown in Table-I. The most common identifiable cause of NC in the present study was BA (38,30.6%). Comparison of Clinical features of BA and Other causes of NC is given in Table- II. Among the studied patients most of the cases were male 95(76.6%). The mean age at onset of jaundice was 6.75±7.3days and mean age at admission was 83.6±40.3days. The presence of persistent pale colored stool was more commonly seen in patients with BA (86.8%) (p 0.000).

Table-I: Etiology of NC Cases (n=124).

Etiology	N (%)
Biliary atresia	38(30.6)
Neonatal hepatitis	
Idiopathic neonatal hepatitis	48 (38.7)
Cytomegalovirus	15(12.1)
Toxoplasmosis	02 (1.6)
Herpes simplex virus	01 (0.8)
Rubella	02 (1.6)
Urinary tract infection	02 (1.6)
Metabolic	
Tyrosinemia	01(0.8)
Galactosemia	01(0.8)
Endocrine	
Hypothyroidism	07(5.6)
Miscellaneous	
Choledochal cyst	03 (3.3)
PFIC	02 (1.6)
Alagille syndrome	01 (0.8)
Down syndrome	01 (0.8)

Table- II: Comparison of Clinical features of BA and Other causes of NC

Clinical Characteristics	Total n = 124 (%)	BA n = 38 (%)	Other causes n = 86 (%)	p value
Sex				
Male	95(76.6)	28 (73.7)	67(77.9)	0.609
Female	29(23.4)	10 (26.3)	19(22.1)	
Age at admission (days)	83.6±40.3	81.5 ± 38.4	85.7±42.1	0.586
Age at onset of Jaundice (days)	6.75±7.3	6.4 ± 7.7	7.1±6.9	0.633
Birth weight (kg)	2.8±0.6	2.9 ± 0.4	2.7±0.5	0.020
Weight at admission (kg)	4.7±0.7	4.8 ± 0.7	4.6±0.6	0.131
Gestational age				
Term	95 (76.6)	35 (92.1)	60 (69.8)	**0.007**
Preterm	29 (23.4)	3 (7.9)	26 (30.2)	
History of consanguinity	8 (6.4)	0 (0.0)	8(9.3)	0.068
Degree of jaundice				
Mild	39 (33.7)	16 (42.1)	23 (27.1)	0.221
Moderate	59 (48.8)	16 (42.1)	43 (54.2)	
Severe	26 (17.5)	6 (15.8)	20 (18.8)	
Pale color stool				
Persistent	52 (41.9)	33 (86.8)	19 (22.1)	0.000
Intermittent	72 (58.1)	5(13.2)	67 (77.9)	-
Liver palpable	124 (100)	38 (100.0)	86 (100.0)	0.000
Liver size (cm)	5.0±1.4	4.3 ± 1.0	5.6±1.7	0.736
Spleen palpable	43 (34.7)	14 (36.8)	29 (39.6)	0.724
Spleen size (cm)	2.6±1.4	2.5 ± 1.5	2.6 ±1.3	0.146
Ascites	19 (15.3)	2 (5.3)	17(19.8)	
Eye examination				
Chorioretinits	3 (2.4)	1 (2.6)	2 (2.3)	0.892
Cataract	5 (4.1)	2 (5.3)	3 (3.5)	
Cardiac murmur	3 (2.4)	3 (7.9)	0 (0.0)	0.048

Discussion:

The diagnosis of Neonatal cholestatic disorder is difficult because of the several possible diagnoses with similar clinical presentation and the lack of specificity of the available diagnostic tests.[6] It is now recommended that BA should be excluded in all term infants who still have jaundice at 3 weeks of age.[7,8]

During the study period, a total of 124 consecutive cholestatic cases were evaluated and their mean age at admission was 83.6±40.3 days and mean age at onset of jaundice was 6.75±7.3days. Majority of the infants with NC were male and this is most probably due to disparity in seeking medical advice between genders. In a previous study in Bangladesh[9] conducted on similar subjects and in the same centre, the mean age at presentation of cases was 105 days while the mean age at onset of jaundice was 5.8 days.

In the present study the most common identifiable cause of neonatal cholestasis was BA (38, 30.6%).This finding is consistent with findings of the study conducted at King's College Hospital, London, England, biliary atresia (35%) and idiopathic neonatal hepatitis (30%) were the most common etiologies respectively.[10]

A tentative diagnosis of Progressive familial intrahepatic cholestasis (PFIC) was made in two male infants presented with jaundice , no family history of cholestatic jaundice and normal GGT but serum bile acid assay or genetic studies could not be done. One male child was diagnosed as Alagille syndrome who had triangular faces and bile duct paucity but did not have any other features of Alagille syndrome. A three months old Female child was admitted with decompensated liver disease with a family history of sibling death at 9 months of age due to jaundice and diagnosis was not confirmed. This child was diagnosed as a case of tyrosinemia as serum alpha fetoprotein was high (>1,00000 ng/ml) and prolonged PT >23 sec. which was not corrected by injection Konakion but enzyme assay could not be done .One case was diagnosed as case of galactosemia due to presence of reducing substances in urine and improvement of jaundice after withdrawing lactose containing diet but RBC galactose-1-phosphate uridyl transferase (GAL-1-PUT) assay could not be done. Galactosemia is a potentially treatable cause of NC.Some metabolic and genetic causes of NC might have been missed due to unavailability of specific diagnostic facilities in the centre.

The present study showed that there was a significant difference between onset of jaundice and hospital admission. It is consistent with the consensus report[11] on Neonatal Cholestasis Syndrome published from India there was a long delay average duration of 4.5 weeks. In the present study, all subjects (100%) had history of passage of pale coloured stool and 52 (41.9%) had history of persistent and rest 72 (58.1%) had intermittent passage of pale colored stool. The present study found that mean birth weight and the frequency of term baby was significantly higher in biliary atresia cases than that having other causes of NC (p 0.020 and 0.007 respectively). The size of the liver in infants with other causes of NC was significantly larger than that of BA cases (p0.000). There was abnormal eye finding among 8cases. Cardiac murmur (pansystolic murmur of VSD) was found in 3 cases with BA though this is not an usual findings in BA.

Conclusion: Among studied subjects Biliary atresia was found to be the most common identifiable cause of neonatal cholestasis. Jaundice with pale colored stool and hepatomegaly was found to be the most common presenting clinical features of neonatal cholestasis. Though jaundice appeared by two weeks of life there was significant delay in seeking medical advice. Laboratory facilities should be made available to identify the definitive etiology of neonatal cholestasis.

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