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Original article

Clinical Characteristics, Biochemical Profile and Etiology of Cholestatic Jaundice in Bangladeshi Infants: A Tertiary Care Hospital Experience.

Khan Lamia Nahid[1], Nazmul Kabir Qureshi[2], Wahiduzzaman Mazumder[3], ASM Bazlul Karim[4]

[1]Junior Consultant, Gastroenterology, 500 Bed Mugda General Hospital, Dhaka, Bangladesh. [2]Specialist, Department of Medicine & Endocrinology, United Hospital Limited, Bangladesh. [3]Assistant Professor, Department of Paediatric Gastroenterology & Nutrition, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. [4]Chairman, Department of Paediatric Gastroenterology & Nutrition, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Abstract:

Background: Biliary atresia (BA) and idiopathic neonatal hepatitis(INH) are the two most common aetiologies of neonatal cholestatic jaundice. Aims: This study has been carried out to find out clinical characteristics, biochemical profile, aetiologies of neonatal cholestasis . Methods: This cross-sectional study was done from March, 2013 through March, 2014 among 60 infants who presented with cholestatic jaundice at the department of Paediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh. Clinical history, physical examination findings were recorded and investigations were done as appropriate. Results: Studied subjects [male n=38 (63.3%), female n=22 (36.7%)] had their mean age at admission 99.5±48.2 days, mean age at onset of jaundice 9.18±8.42 days, hepatomegaly (100% cases), splenomegaly (40% cases), direct S. bilirubin 8.75±2.62 mg/dl, ALT 150.16±99.85 U/L and hemoglobin 9.08±1.72 gm/dl. Scintigraphy was found positive in 22 (36.7%). Histopathology findings of 54.5% liver biopsies were consistent with biliary atresia. Mean of total, direct and indirect serum bilirubin and ALT were significantly different between subjects with BA and idiopathic neonatal hepatitis (INH). Mean of serum direct bilirubin and serum ALT was more in subjects of INH (p 0.03 & p 0.003). Conclusion: Biliary atresia was found to be the most common cause of neonatal cholestasis among studied subjects. Most of the cases presented late and early referral of these cases is important for effective evaluation and judicious management.

Key words: Cholestatic Jaundice, Bangladeshi infants

Introduction :

Jaundice is the most overt physical sign of liver disease and occurs more commonly in the neonatal period than at any other time of life [1]. Neonatal cholestasis is a group of hepato-biliary disorders occurring within the first three months of life and is characterized by direct bilirubin value greater than 1.0 mg/dl (>17 μmol/L) when total bilirubin is less than 5 mg/dl or direct bilirubin of more than 20% of total when the total bilirubin is greater than 5 mg/dl (>85 μmol/L)[2,3]. Unfortunately, misdiagnosis of cholestasis as physiological jaundice delays the identification of important liver diseases and substantially impairs long term health outcome.

Up to 15% of breast fed infants experience jaundice lasting for more than 3 weeks.[4] Neonatal cholestasis occurs in 0.04% to 0.2% of live births[3,5] that arises from abnormalities in the uptake, handling, transport and excretion of bile salts and bilirubin by hepatocytes or in the flow of bile through the bile canaliculi and ducts [6.] Biliary atresia (BA) and idiopathic neonatal hepatitis are the two most common aetiologies of neonatal cholestatic jaundice. In a study of these conditions accounted for 35% and 30% of cases respectively.[7] Other causes included α1- antitrypsin deficiency (17%), Alagille syndrome (6%), choledochal cyst (3%), progressive familial intra-hepatic cholestasis(PFIC).[7,8] BA is the most common single indication for liver transplantation in children.[9] A recent retrospective cohort study from Canadian Paediatric Hepatology research Group (CPHRG) estimated the incidence of biliary atresia in Canada to be 1 in 19065 (5.25 per 1,00,000 live birth).[10] Approximately, 60% to 70% of patients with biliary atresia will develop cirrhosis and will require liver transplantation during childhood.[10, 11] and 50% of them will require it within first two years of life.[12]Multiple cohort studies have reported that infants surgically treated for biliary atresia before three months of age had overall survival of up to 15 years of age.[13]

Aim Of Study :

This study has been carried out to find out clinical characteristics, biochemical profile and etiologies of neonatal

cholestasis among Bangladeshi infants, its time of presentation and time interval of diagnosis.

Materials And Method:

This cross-sectional study was carried out from March, 2013 through March, 2014 among infants presented with cholestatic jaundice at the department of Paediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University. A total of 60 infants with jaundice persisting beyond 2 weeks of age, where jaundice developed before three months of age, were studied who fulfilled the following criteria: (1) direct reacting bilirubin of ≥ than 1 mg/dl, if total serum bilirubin is <5 mg/dl, (2) direct reacting bilirubin > 20 % of total serum bilirubin, if total serum bilirubin is > 85 µmol/L (5.0mg/dl), (3) pale stool, either persistent or intermittent and (4) dark urine. Infants with jaundice developed after three months of age, jaundice due to unconjugated hyperbilirubinemia and those suffering from severe co-morbid conditions were excluded from the study. Detailed clinical history was taken and physical examination was done. Investigations included: S. Bilirubin, ALT, PT, Gamma glutamyl transpeptidase(GGT), IgM antibody of TORCH, FT4, TSH level, urine R/E and culture, hepatitis B serology, urine for reducing substance, abdominal ultrasound before a liver biopsy. Hepatobiliary scintigraphy using technetium-labeled iminodi-acetic acid analogues was used to differentiate biliary atresia from non obstructive causes of cholestasis. Percutaneous liver biopsy using Tru-cut biopsy needle was done and was interpreted by a single pathologist of BSMMU with experience in paediatric liver disease. Written informed consent was taken from every patient's parents and Study protocol was approved by the Institutional Review Board, BSMMU. Statistical analysis was done by Statistical Package for Social Science (SPSS Inc, Chicago, Illinois, USA) software version 20 for windows.

Results :

Clinical characteristics, biochemical profile and etiology of 60 cholestatic cases [male n=38 (63.3%) and female n=22 (36.7%)] were studied. Their mean age at admission was 99.5±48.2 days and mean age at onset of jaundice was 9.18±8.42 days. The mean weight at admission was 4.19±1.27 kg and mean birth weight was 2.61±.49 kg. Among studied subjects, 44 (73.3%) were term baby and rest (26.7%) were preterm. History of consanguinity of marriage was present in 10 (16.7%) cases and no sibling of patients was affected by similar type of illness.

All (100%) had history of passage of pale stool; 26 (43.3%) had persistent and rest (56.7%) had intermittent nature. All (100%) had hepatomegaly and splenomegaly was found in 24 (40%) studied subjects. Ascites was found in 12 (20%) subjects and 5 (3%) had edema. Fifty-one (85%) had normocephely, 7 (11.7%) microcephaly and 2 (3.3%) macrocephaly. Two (2) subjects had chorioretinits and one (1) had cataract. Cardiac murmur of VSD was found in 2 cases. Facial dysmorphysim was found in 2 of 60 patients (Down's facies and hypothyroid facies).

Liver function, hematological and thyroid function tests were done in all studied subjects (***Table-I***).

Table I: Liver Function, hematological and thyroid function tests of Studied Subjects (n=60).

Tests	**Mean ± SD (N=60)**	**95% CI**
Total S. bilirubin (mg/dl)	11.77±3.99	10.69-12.86
Direct S. bilirubin (mg/dl)	8.75±2.62	8.01-9.34
Indirect S. bilirubin (mg/dl)	3.04±2.51	2.41-3.69
ALT (U/L)	150.16±99.85	128.07-178.29
GGT (U/L)	539.05±568.34	396.47-717.29
INR	1.77±1.43	1.41-2.41
Hemoglobin (gm/dl)	9.08±1.72	8.59-9.54
TC of WBC (/cmm)	13006.83±3773.33	12234.01-14218.22
Platelet count (/cmm)	272216.67±115415.25	233668.01-306649.66
FT4 (pmol/L)	14.61±3.48	13.69-15.57
TSH (mIU/L)	5.21±9.27	3.78-9.29

Scintigraphy was found positive in 22 (36.7%) of 47 patients and thirteen cases did not undergo scintigraphy study. TORCH infection was found positive in 17 (28.3%) cases. Because of lack of parental consent, coagulopathy, huge ascites, etc. liver biopsy was done only in 22 out of 60 cases.(***Table II***).

Table II: Liver Biopsy Findings of Studied Subjects (n=22)

Findings	**Diagnosis**	**Frequency (%)**
Ductular proliferation, bile plugs, intraportal fibrosis	Biliary atresia	12 (54.5%)

Chronic inflammatory cell infiltration, giant cell transformation	Idiopathic neonatal hepatitis	08 (36.4%)
Ductular proliferation, bile plugs, hepatocytes surrounded by fibrous bands	Biliary atresis with biliary cirrhosis	02 (9.1%)

N.B.: Histopathology findings of 54.5% liver biopsies were consistent with biliary atresia.

Aetiology of cholestatic jaundice was determined upon clinical history, examination findings, biochemical parameters, imaging study and liver biopsy results. (***Table-III***)

Table III : Aetiology of Studied Cholestatic Cases (n=60).

Aetiology	**Number (%)**
Biliary atresia	19 (31.6%)
Neonatal hepatitis	14 (23.3%)
Cytomegalovirus	09 (15%)
Toxoplasmosis	02 (3.3%)
Herpes simplex virus	01 (1.7%)
Rubella	01 (1.7%)
Urinary tract infection	01 (1.7%)
Idiopathic neonatal hepatitis	19 (31.6)
Miscellaneous	8 (13.3%)
Choledochal cyst	02 (3.3%)
Hypothyroidism	04 (6.7%)
PFIC	01 (1.7%)
Down syndrome with hypothyroidism	01 (1.7%)
Total	60 (100%)

Grouping of the Studied Subjects According to Etiology: Studied subjects were divided into three groups. Group-I (n=19) included subjects having biliary atresia, Group-II (n=33) included subjects having neonatal hepatitis(NH) and idiopathic neonatal hepatitis and Group-III (n=8) included Misc. causes, In group I, 10 (52.6%) cases were male and rest (47.4%) female. In group II, 22 (66.7%) were male and rest (33.3%) female (p 0.24)

Between Group-I and Group-II, age at admission in days (101.37±55.39 and 99.73±46.56; p 0.91), age at onset of jaundice in days (8.11±6.10 and10.42±10.11, p 0.36) and weight of subjects at admission in Kg (4.39±.86 and 4.06±1.36, p 0.35) were not statistically significant. Birth weight in kg was more in Group-I (2.81±0.28) than in Group-II (2.54±0.46) (p 0.02). Preterm babies were more in Group-II than in Group-I (42.4% vs 0%, p 0.001). History of consanguinity of marriage was more in Group-II than in Group-I (21.2% vs 0%, p 0.03).

Clinical Characteristics between group-I and group-II were as follows: Frequency of persistant: 100% and 12% (p 0.001); intermittent pale stool: 0% and 88% (p 0.001); normocephaly: 100% and 81.9% (p 0.040); Splenomegaly: 15% and 61% (p 0.002); ascites: 21.2% and 21.2% (p 0.98); edema: 10.5% and 9.1% (p 0.86). Hepatomegaly was present in all(100%) cases in both groups. Scintigraphy was significantly positive (n=19, 100%) in group I than in group II (n=1, 3%) subjects (p 0.001)**.** Scintigraphy was not done in 9 subjects with NH & INH.

Total S. bilirubin, direct S. bilirubin, indirect S. bilirubin were more in Group II than in Group I (p 0.03). S. ALT was more in group-II than in group-I (p 0.003) Comparison of complete blood count and thyroid function tests between Group-I and Group II were not statistically significant. ***(Table IV)***

Table IV: complete blood count, LFT and thyroid function tests between Group-I and Group II

	Biliary atresia Group I (n=19)	**NH and INH Group II (n=33)**	
LFT, CBC and TFT	**Mean ± SD (95% CI)**	**Mean ± SD (95% CI)**	**p valve**
Total S. bilirubin (mg/dl)	9.98±2.22 (8.91-11.06)	13.29±4.42 (11.72-14.86)	0.004
Direct S. bilirubin (mg/dl)	7.92±2.06 (6.93-8.92)	9.51±2.69 (8.56-10.47)	0.03
Indirect S. bilirubin (mg/dl)	2.17±1.19 (1.59-2.74)	3.76±2.94 (2.71-4.80)	0.03
ALT (U/L)	109.31±56.82 (81.92-136.70)	192.82±109.43 (154.01-231.62)	0.003
GGT (U/L)	695.47±535.17 (437.53-953.42)	516.42±628.79 (293.46-739.38)	0.30
INR	1.55±.63 (1.24-1.85)	2.05±1.82 (1.40-2.70)	0.25
Hemoglobin (gm/dl)	9.37±1.53 (8.64-10.11)	8.97±1.78 (8.34-9.60)	0.40
TC of WBC (/cmm)	13026.32±3750.83 (11218.47-14834.16)	13070.00±4058.06 (11631.07-14508.93)	0.97
Platelet count (/cmm)	254473.68±95348.69 (208517.08-300430.29)	287212.12±131815.86 (240472.25-333951.99)	0.35
FT4 (pmol/L)	15.38±3.19 (13.84-16.91)	15.02±2.59 (14.11-15.95)	0.66

TSH (mIU/L)	3.59±1.04 (3.08-4.09)	3.82±.91 (3.50-4.14)	0.40

Discussion :

This hospital based cross sectional study was carried out to determine the etiology and clinical profile of cholestatic jaundice in infancy. During the study period, a total of 60 consecutive cholestatic cases were evaluated and their mean age at admission was 99.5±48.2 days and mean age at onset of jaundice was 9.18±8.42 days. In a previous study[14] conducted on similar subjects and at 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. A consensus report[15] observed that there was a long delay by parents in seeking medical attention for their affected infants with an average duration of 4.5 weeks and the average age at presentation to a specialized center was 3.5 months (ranging from birth to 15 months) with a consequent delay of 3 months for referral to medical and surgical centers. Reported study revealed that the mean age at onset of jaundice was significantly lower in cases of biliary atresia when compared to idiopathic neonatal hepatitis cases (9±13 days versus 20±21 days; p 0.032).[16] But it is inconsistent with the result of present study (p 0.36)..

In two similar studies,[7,17] it was found that either inadequate follow-up or reassurances by primary health care providers that the jaundice was physiologic was the commonest cause of late referral. To help reduce the average age for diagnosis of biliary atresia, several groups in Japan and Taiwan have developed pilot programs in which stool color cards are given to mothers of newborns.[18]

Alagille in his study identified several variables that are useful in evaluating the cholestatic jaundice.[19] The study consisted of 288 infants. Subjects having intrahepatic cholestasis and subjects having biliary atresia, the frequency of male gender was 66% and 45% respectively and birth weight was 2680 grams and 3230 grams respectively.[20] The present study found that mean birth weight was less in subjects having neonatal hepatitis and idiopathic neonatal hepatitis (2.54±.46 kg) than that of subjects having biliary atresia (2.81±.28 kg) (p 0.02).

In the present study, all subjects (100%) had history of passage of pale stool: 26 (43.3%) had history of persistent and rest (56.7%) had intermittent passage of pale colored stool. All subjects (100%) had hepatomegaly. Splenomegaly was found in 24 (40%) studied subjects. Ascites was found in 12 (20%) subjects and 5 (83%) had edema. In a similar study[14], history of persistent passage of pale stool was found more among subjects having biliary atresia (81.3%) than subjects having NH and INH (43.2%), and passage of intermittent pale stool was found more frequently among subjects having NH & INH (32.2% vs 18.8%). Frequency of hepatomegaly was almost similar in both groups (NH & INH: 86.5% and BA: 87.5%). Splenomegaly (73% vs 62.5%) and ascites (13.5% vs 6.2%) was more frequent among subjects having NH & INH. In the present study, in group-I (BA) and group-II (NH and INH), frequency of persistant pale stool was 100% and 12% and intermittent pale stool was 0% and 88% (p 0.001). Splenomegaly was present in 3 (15%) patients in group-I and 20 (61%) patients in group-II (p 0.002).

In the present series, 19 (31.6%) had biliary atresia, 14 (8.4%) neonatal hepatitis [CMV 9 (5.4%), toxoplasmosis 2 (1.2%), HSV 1 (0.6%), rubella 1 (0.6%), UTI 1 (0.6%)] and 19 (31.6%) had idiopathic neonatal hepatitis. In a study conducted at King's College Hospital, London, England, biliary atresia and idiopathic neonatal hepatitis were the most common etiologies and these conditions accounted for 35% and 30% of cases respectively.[20]

In the present series, mean total S. bilirubin was 9.98±2.22 mg/dl in infants with biliary atresia and 13.29±4.42 mg/dl in infants with neonatal hepatitis and idiopathic neonatal hepatitis (p 0.004). In a similar study, levels of serum bilirubin was reported as 10.4 mg/dl and 14.1 mg/dl in cases of biliary atresia and neonatal hepatitis respectively.[14] In a study on 65 patients with neonatal cholestasis, found no significant difference of the level of liver enzymes between BA and NH group.[20] But in the present study, ALT was found higher in NH & INH group than in BA group (p 0.003).

Scintigraphy was significantly positive (n=19, 100%) among BA Group than NH & INH Group (n=1, 3%) (p 0.001). Similar findings were observed by others.[3, 21]

A retrospective study showed that biliary atresia was the most frequent biopsy-driven diagnosis, found in 58.2% cases, followed by intrahepatic bile duct paucity found in 10.9% cases, metabolic disease in 10.9% cases, INH in 9.1% cases and liver cirrhosis in 3.6% case.[22] In the present study, liver biopsy was done only in 22 out of 60 cases. The histologic features of BA are ductular proliferation, bile plugs and intrahepatic fibrosis. The features of INH are chronic inflammatory cell infiltration, giant cell transformation, and the features of biliary cirrhosis are hepatocytes surrounded by fibrous bands.[23]

Limitations Of The Study:

Sample size of this study was small due to limitations of time and resources.

Conclusion :

New born babies having jaundice beyond 14 days of age with dark urine and acholic /pale stools should be investigated to rule out conjugated hyperbilirubinemia and prompt referred to

appropriate health facilities should be made for further investigations and treatment. Biliary atresia was found to be the most common cause of neonatal cholestasis among studied subjects. Most of the cases presented late though jaundice appeared by two weeks of life. Early referral of these cases is important for effective evaluation and judicious management.

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