Original Article

Clinico-Etiological Study of Cholestatic Jaundice in Infancy

DOI: dx.doi.org

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Received: 7 January 2024
Accepted: 23 January 2024
Published: 10 February 2024

Published by:
Sher-E-Bangla Medical College, Barishal, Bangladesh

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Editor: Prof. Dr. HN Sarker

Available Online:
https://bdjournals.org/index.php/planet/article/view/412

ABSTRACT

Introduction: *Cholestatic jaundice in infancy especially neonatal cholestasis is the most common liver problem in infants and one of the most problematic challenges for pediatricians. Neonatal cholestasis has a number of causes, and accurate diagnosis is important in guiding appropriate therapy either surgical or medical.* ***Aim of the study:*** *This study aimed to identify the etiology and clinical profile of cholestatic jaundice in infancy.* ***Methods and materials:*** *This cross-sectional observational study was conducted at the Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from January 2021 to January 2022. A total of 30 cases were selected purposively. Statistical analysis was done by using SPSS (Statistical Package for Social Science) version 20.* ***Result:*** *Biliary atresia (66.7%) was the commonest cause of cholestatic jaundice followed by idiopathic neonatal hepatitis (INH) (26.7%) & neonatal hepatitis (NH) (6.6). Jaundice, intermittent or persistent pale stool, and dark urine were found in all the cases, and hepatomegaly and splenomegaly were found in 95%, and 60% of cases respectively in biliary atresia (BA) and in 80% and 70% of cases respectively in NH and INH. Mean serum bilirubin was 11.7+3.6 mg/dl in infants with BA and 16.1+13.8mg/dl in those with NH and INH.* ***Conclusion:*** *This study concludes that biliary atresia is the most common cause of neonatal cholestasis. Most of the cases present late though jaundice appears by two weeks of life. So, early referral of these cases is important.*

(The Planet 2023; 7(1): 113-123)

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Keywords: *Cholestatic jaundice, Infancy, Idiopathic neonatal hepatitis, Biliary atresia*

INTRODUCTION

Neonatal cholestasis is defined as prolonged elevation of serum level of conjugated bilirubin (> 2 mg dL or >20% of the total bilirubin) beyond the first 14 days of life [1]. Neonatal cholestasis can be due to infectious, genetic, metabolic, or undefined abnormalities giving rise to mechanical obstruction of bile flow or functional impairment of hepatic excretory function and bile secretion. The common causes of neonatal cholestasis are idiopathic neonatal hepatitis and biliary atresia [2]. The overall incidence of neonatal liver disease manifesting clinical or biochemical evidence of cholestasis is approximately 1 in 2,500 live births [3]. The incidence of BA found in various Western-based literature is around 0.52 to 0.71 per 10,000 live births. However, it is much more common among East Asians. Thus, in a recent epidemiological study from Korea, the estimated incidence was 1.06 per 10,000 live births [4]. Neonatal hepatitis (NH) is defined as intrahepatic cholestatic disorders other than structural disorders of the biliary tree. Idiopathic neonatal hepatitis (INH) is defined as intrahepatic cholestasis in which the characteristic giant-cell hepatitis lesion is present on liver biopsy but for which no cause (infectious, genetic, metabolic, or anatomic) is identified. Another important cholestatic disorder is paucity of intrahepatic bile ductules [5]. Neonatal cholestasis usually presents with prolonged jaundice, pale stool (persistent/intermittent), dark urine, and hepatomegaly. Infants with severe liver disease may also present with encephalopathy, which might be difficult to diagnose in the neonatal period because it may manifest with nonspecific symptoms like poor feeding and sleep disturbances. Bleeding and bruising due to vitamin K deficiency are another presentation of severe liver disease. Far less common is the presentation of seizures from hypoglycemia or hypocalcemia secondary to vitamin D deficiency [6]. The early diagnosis of cholestatic liver disease is one of the major challenges for pediatricians when evaluating jaundice in infants. Early recognition of liver disease greatly facilitates the care and outcome of infants, because several serious life-threatening disorders may have cholestasis as a major presenting sign of underlying neonatal liver disease. A key component of the work-up is the measurement of fractionated bilirubin levels. An elevation of conjugated bilirubin fraction should prompt the clinician to initiate a work-up to determine the cause of neonatal cholestasis. In general, if a patient is developing progressive jaundice soon after birth and is still jaundiced at 2 weeks of life, or develops jaundice within 3 months of life, a work-up for neonatal cholestasis should begin [7]. Cholestatic jaundice in early infancy has a wide variety of causes. Idiopathic neonatal hepatitis and biliary atresia are not only the most important ones causing neonatal cholestasis but also pose the greatest diagnostic dilemma. The differentiation between biliary atresia and idiopathic neonatal hepatitis is more crucial since the former needs urgent intervention [8]. So early and proper diagnosis of neonatal cholestasis is important for proper management because

some causes are treatable and some causes are preventable [5]. The study will help to identify the etiology and common clinical presentations of cholestatic jaundice in infants and it will also help early recognition of neonatal cholestasis.

OBJECTIVE

General Objective

- To find out the etiology and clinical presentations of cholestatic jaundice in infancy.

Specific Objectives

- To determine the biochemical and hematological parameters of neonatal cholestatic cases.
- To determine the imaging feature of the cholestatic cases.
- To compare clinical and biochemical features of biliary atresia and neonatal hepatitis in infancy.

METHODS AND MATERIALS

This cross-sectional observational study was conducted at the Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from January 2021 to January 2022. All admitted infants in the respective department were considered as the study population. A total of 30 cases were selected purposively for this study as per inclusion and exclusion criteria.

Inclusion Criteria

- Infants below 12 months.
- Infants who developed jaundice before 3 months of age and persisted for > 2 weeks.
- Infants with intermittent or persistent pale stool.
- Infants who passed of dark urine.
- Infants with bilirubin concentration more than 20% of total bilirubin or more than>2mg/dl.
- Infants whose guardians had given consent to participate in the study.

Exclusion Criteria

- Infants who developed jaundice after 3 months of age.
- Infants whose guardians did not give consent to participate in the study.

Detailed history, thorough physical examination, and relevant investigations were done. Data were collected on a pre-designed semi-structured questionnaire. Statistical analysis was done by using SPSS (Statistical Package for Social Science) version 20. All the values were expressed as mean ± SD; the Student's unpaired t-test was used as a statistical tool. P-value <0.05 was considered as significant. Analyzed data were presented in tables and diagrams. Informed written consent was obtained from the guardians of each infant. Ethical clearance was taken from the ethics committee of BSMMU.

RESULTS

Table I: Etiology of studied patients (N=30)

Etiology	n	%
Biliary atresia	30	66.7
Neonatal hepatitis	02	6.70
Cytomegalovirus	01	3.33
Herpes simplex	01	3.33

virus		
Idiopathic neonatal hepatitis	08	26.67

Biliary atresia was the commonest (66.7%) cause of neonatal cholestasis followed by idiopathic neonatal hepatitis (23.3%) and neonatal hepatitis (6.7%). ***[Table I]***

Table II: Age distribution of studied patients (N=30)

Types of patients	**n**	**Mean age± SD (Days)**
Biliary atresia	20	126.5±81.44
*NH & INH	10	105±16.01
Total	30	118.33±67.69

**NH=Neonatal hepatitis; INH= Idiopathic neonatal hepatitis*

The mean age at admission of biliary atresia cases was 126.5±81.4 days and that of neonatal hepatitis and idiopathic neonatal hepatitis was 105±16.01 days. The overall mean age at admission of cholestatic jaundice cases was 118.3±67.7 days. ***[Table II]***

Table III: Gender distribution of the study subjects (N=30)

Gender	**Biliary atresia n (%)**	**INH n (%)**	**NH n (%)**	**Total n (%)**
Male	16 (84.21)	03 (15.80)	0 (0.0)	19 (100.0)
Female	04 (36.40)	05 (45.5)	02 (18.1)	11 (100.0)
Total	**20 (66.7)**	**08 (26.6)**	**02 (6.7)**	**30 (100.0)**

Nineteen patients were males and eleven were females. Biliary atresia cases were found more in males and neonatal hepatitis cases were found more in females. ***[Table III]***

Table IV: Distribution of patients according to age at onset of symptoms and age at admission (N=30)

Age	**Biliary atresia (n=20) Mean± SD**	**NH & INH (n=10) Mean± SD**
Age at onset (days)	09.4 ±8.64	15.0±5.64
Ae at admission (days)	126.5±81.44	105.6 ±16.01

Delay (days)	117.10±73.5	99 ±12.67

The mean age at onset of jaundice was 9.41±8.64 days and the mean age at admission was 126.5±81.44 days in case of biliary atresia. The mean age at onset of jaundice was 15.0±5.64 days and the mean age at admission was 105.6±16.01 days in the case of INH & NH. Thus, an overall delay in seeking treatment was 117.10 ± 73.5 days in biliary atresia and 99±12.67 days in NH and INH. ***[Table IV]***

Table V: Birth weight of biliary atresia and NH and INH patients (n=12)

Diagnosis	n	Birth weight (gm) (Mean± SD)	p-value
Biliary atresia	7	2771.43±186.76	0.001*
NH & INH	5	2180±238.75	

Unpaired Student's t-test; *p-value was significant

Out of 30 patients, birth weight was available in 12 patients and that of 18 patients was not known due to home delivery. The mean birth weight of biliary atresia cases was 2771.4±186.76 gm and that of NH and INH cases was 2180±238.75 gm. The mean difference in birth weight was statistically significant. Infants with biliary atresia had significantly higher birth weight than those with NH & INH. ***[Table V]***

Table VI: Gestational age at birth of the respondents (N=30)

Gestational age	Biliary atresia n (%)	NH & INH n (%	Total
Term	17 (85.0)	04 (40.0)	21
Preterm	03 (15.0)	06 (60.0)	09

17 (85%) patients were term and 03 (15%) were preterm in biliary atresia but 4 (40%) were term and 6 (60%) were preterm in NH and INH. Most of the patients in the biliary atresia group were term infants. ***[Table VI]***

Table VII: Clinical characteristics of infants of BA, NH, and INH (N=30)

Clinical characteristics	Biliary atresia n (%)	NH & INH n (%)
Jaundice	20 (100.0)	10 (100.0)
Dark urine	20 (100.0)	10 (100.0)

Persistent alcoholic stool	18 (90.0)	02 (20.0)
Intermittent alcoholic stool	02 (10.0)	07 (70.0)
Hepatomegaly	19 (95.0)	08 (80.0)
Splenomegaly	12 (60.0)	07 (70.0)
Purpura, ecchymoses, petechiae	01 (5.0)	0 (0.0)
Ascites	02 (10.0)	01 (10.0)
Encephalopathy	01 (5.0)	0 (0.0)

Jaundice and dark urine were found in all cases of both biliary atresia neonatal hepatitis and idiopathic neonatal hepatitis. Persistent acholic stool was an important finding of biliary atresia and it was found in 18 (90%) cases. Intermittent acholic stool was a significant finding of NH and INH and it was found in 7 (70%) cases. In biliary atresia 19 (95%) patients were found to have hepatomegaly and the liver was firm to hard in consistency. Eight (80%) patients with NH and INH were found to have hepatomegaly. Splenomegaly was commoner in NH and INH than biliary atresia. Purpura, ecchymoses, and petechiae were found in one infant with biliary atresia but none in NH and INH cases. Ascites were seen in 2 patients with biliary atresia and one case of INH. Hepatic encephalopathy also was observed in one patient with biliary atresia. ***[Table VII]***

Table VIII: Liver function tests in studied infants with BA, NH, and INH (N=30)

Liver function tests	**Biliary atresia (n=20) (Mean± SD)**	**NH & INH (n=10) (Mean± SD)**	**p-value**
Serum total bilirubin (mg/dl)	11.7±3.6	16.1±13.8	0.24
Serum direct bilirubin (mg/dl)	6.8 ±3.0	9.6±9.8	0.30
ALT(U/L)	237.9±197.3	324.8±184.0	0.19
Alkaline phosphates (U/L)	1088.9±421.2	607.5±323.5	<0.01*
Gamma-glutamyl transpeptidase (GGT) (U/L)	697.5±278.0	541.6+218.4	0.07
INR	1.2±0.2	1.5±0.6	0.05*
Serum albumin (gm/L)	31.9±7.9	30.8±7.7	0.07

*Unpaired students t-test; *Significant*

In biliary atresia, the mean serum total bilirubin was 11.7±3.6 mg/dL, and in NH and INH was 16.1±13.8 mg/dL and the difference between these two values was not significant. Serum ALT was 237.9±197.3 U/L and 324.8±184.0 U/L in

biliary atresia and NH and INH cases respectively which was not statistically significant. Mean serum alkaline phosphatase was 1088.9±421.2 U/L in biliary atresia and 607.5±323.5 U/L in NH and INH cases which was significant ($p<0.01$). Gamma-glutamyl transpeptidase, prothrombin time, and serum albumin level showed no significant difference between biliary atresia and NH and INH groups. ***[Table VIII]***

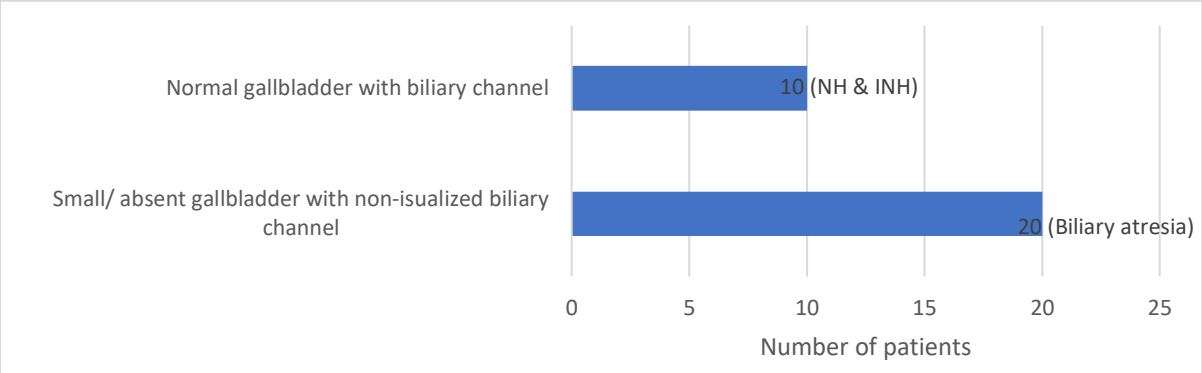

Figure I: Ultrasonographic findings of the respondents (N=30)

In biliary atresia, the gallbladder was either small in size or absent or bile channels were not visualized and no contraction of the gallbladder was seen even after meals. On the contrary, in neonatal hepatitis, the gallbladder was normally visualized with biliary channels, and contraction of the gallbladder was seen after meals. ***[Figure I]***

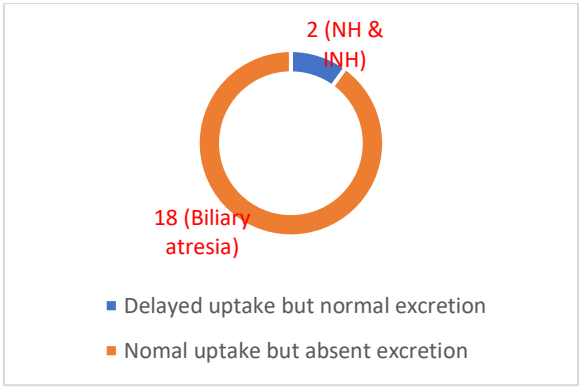

Figure II: Findings of hepatobiliary scintigraphy (N=30)

Hepatobiliary scintigraphy was done in 20 cases of which 2 patients showed delayed uptake but normal excretion, it was consistent with NH and INH. Eighteen infants showed normal uptake of the isotope but absent excretion into the biliary channels and intestine which was consistent with biliary atresia. ***[Figure II]***

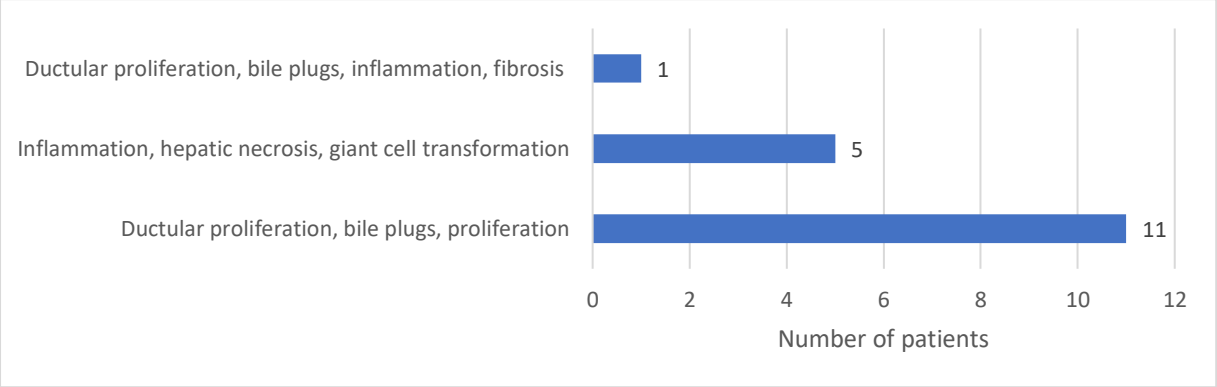

Figure III: Liver biopsy findings of the study subjects (N=30)

A liver biopsy was done on 17 infants. Typical features of biliary atresia were found in 11 cases. 5 patients showed features of idiopathic neonatal hepatitis and 1 patient showed features of early biliary cirrhosis. ***[Figure III]***

DISCUSSION

In the present series of cholestatic jaundice, biliary atresia was found in 20 (66.7%) cases, neonatal hepatitis 2 (6.6%) cases, and idiopathic neonatal hepatitis 8 (26.7%) cases. A retrospective study conducted in Bangladesh by Karim & Kamal et al. They reported biliary atresia in 16 (25.8%) cases, neonatal hepatitis in 22 (35.5%) cases, and idiopathic neonatal hepatitis in 15 (24.2%) cases. They found neonatal hepatitis as the commonest cause of cholestatic jaundice but in the present study, biliary atresia was found as the commonest cause of cholestatic jaundice [5]. According to an Indian study by Matthai & Paul et al, 14 (38.8%) cases were found to have neonatal hepatitis 7 (19.4%) cases of biliary atresia, and 4 (11%) cases were found to have idiopathic neonatal hepatitis [9]. These findings were inconsistent with our findings. The mean age at admission to the hospital of the biliary atresia case was 126.5181.4 days, though the mean age of onset of jaundice was 9.4 days and the average delay was 117.1+73.5 days. Karim & Kamal et al reported the mean age at presentation to the hospital in their series was 105 days while the mean age at onset of jaundice was 5.8 days and the average delay was 99.2 days [5]. These findings are almost consistent with our findings. Another study from India carried out by Yachha & Sharma et al was also consistent with the present study [10]. The mean birth weight of biliary atresia cases was 2771.4+186.76 gm and that of NH and INH cases was 2180 +238.75 gm. On the other hand (85%) of patients were term and (15%) were preterm in biliary atresia but (40%) were term and (60%) were preterm in NH and INH. So, in this study, NH and INH were common in preterm, small for gestational age, or low birth weight infants. Intrauterine infection and metabolic diseases are the most important causes of neonatal hepatitis. Common presenting clinical symptoms of the studied cases were jaundice (100%) and dark urine (100%) found in both biliary atresia and NH or INH cases. Persistent acholic stool was found in 90% of infants

with biliary atresia and 22.2% of infants with NH or INH. Intermittent acholic stool was seen in 10% of cases of BA and 77.8 % of cases of NH and INH. These findings were similar to the findings of Karim & Kamal et al. [5] Common presenting signs of the studied cases of biliary atresia were hepatomegaly (95%), splenomegaly (60%), ascites (10%), purpura (5%), and encephalopathy (5%). The liver was found firm to hard in consistency. In NH and INH hepatomegaly was found in 80% of cases, splenomegaly in 70% of cases, ascites in 10% of cases and examination of the eye was unremarkable in all infants. These findings were similar to the findings of Karim & Kamal et al as well [5]. Biliary atresia was reported to be commoner in female infants in a study by Sokol et al [11]. However, in this series, it was found common in males (16 of 19). This was consistent with a Bangladeshi study. This male preponderance in this series may be due to more parental concern about their male infants [5]. In the present series, the mean bilirubin was 11.7 mg in infants with biliary atresia and 16.1 mg/dl in those with NH or INH. These levels of serum bilirubin are consistent with the findings of Karim & Kamal et al who reported 10.4 mg/dl and 14.1 mg/dl in cases of biliary atresia and neonatal hepatitis respectively [5]. Matthai & Paul et al studied 36 patients with neonatal cholestasis and observed ALT elevation more (mean 235 U/L) in neonatal hepatitis and an alkaline phosphatase elevation more (mean 1793.42 U/L) in biliary atresia cases [9]. Karim & Kamal et al also reported an ALT elevation more (mean 294.4 U/L) in NH and INH and an alkaline phosphatase rise more (mean 767.1 U/L) in biliary atresia cases [5]. Our findings were consistent with the above study where elevation of ALT (mean 224.8 U/L) in NH or INH and alkaline phosphatase level (mean 1088.9 U/L) in biliary atresia cases were observed. Our findings were also similar to another study [12]. In biliary atresia gallbladder was either small in size or absent or bile channels were not visualized and no contraction of the gallbladder was seen even after meals. On the contrary, in neonatal hepatitis, the gallbladder was normally visualized with biliary channels, and contraction of the gallbladder was seen after meals. These findings were consistent with the findings of other studies [2, 5]. Visualization of a normal gall bladder while fasting and contraction after a meal virtually rule out biliary atresia. But the reverse is not always true [13]. Hepatobiliary scintigraphy was done only in 20 infants in the present series. Two patients showed delays. uptake but normal excretion which is consistent with NH and INH. 18 infants showed normal uptake of the isotope but absent excretion into the biliary channels and intestine which was consistent with biliary atresia. Similar findings were also observed by other authors [14, 2]. In a biopsy, typical features of biliary atresia were found in 11 cases, and features of early biliary cirrhosis in 1 infant. Five patients showed features of idiopathic neonatal hepatitis. These findings were consistent with another study [5]. Delays in diagnosis of cholestatic disorders contribute to an increase in morbidity and mortality and also to poor outcomes [15].

LIMITATIONS OF THE STUDY

The study was conducted in a single hospital with a small sample size for a

short duration. So, the results may not represent the whole community.

CONCLUSION

This study concludes that biliary atresia is the most common cause of cholestasis. Moreover, neonatal cholestasis usually presents with prolonged jaundice, pale stool (persistent/intermittent), dark urine, and hepatomegaly.

RECOMMENDATION

Primary health care providers should be educated to asses all infants with jaundice, pale stool, dark urine, or enlarged liver at 2 weeks of age for early referral to a higher center for evaluation and management. Moreover, further studies should be conducted involving a large sample size and multiple centers.

FUNDING

No funding sources

CONFLICT OF INTEREST

None declared

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee

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