Original Article

Aetio-Clinical Profile of Cholestatic Jaundice During Infancy- Study of 30 Cases in a Tertiary Care Hospital.

F Hamid[1], A Afroza[2], P C Ray[3]

Abstract:

Cholestasis in young infants has a varied etiology. There is considerable delay in presentation of cholestatic cases, both in India (average delay of 3 months in referral centers) and Bangladesh (3.5 months). Early diagnosis is important as the effects of cholestasis are profound and wide-spread. EHBA comprises a significant proportion of cases of cholestatic diseases. If treatment of EHBA is delayed beyond the first 90 days of life, the only option thereafter is liver transplantation, which is not presently feasible on a large scale in developing countries. So, the aim and objective of this study is to determine the cause and to categorize the clinical profile and treatment options of conjugated hyperbilirubinaemia in infancy. A total of 30 patients, who fulfilled inclusion and exclusion criteria were included. A detailed history and physical examination was done daily. Complete blood count, liver function tests, HBsAg and TORCH screening, thyroid function test, Urine was tested for non-glucose reducing substances. Ultrasonography of the hepatobiliary system and hepatobiliary scintigraphy was done. Liver biopsy was done in appropriate patients. Patients were followed up daily during hospital stay. The management and its response were also monitored and recorded. Out of 30 patients 24 (80%) were male and 6 (20%) were female. 63% were term and 37% were preterm. Out of 12 patients in BA, 11 were term and only 1 was preterm, whereas in NH group, out of 18 babies, 10 were preterm. Most of the patients were male in both studied groups. Mean value of birth weight in BA was 2.65±0.13 and in NH was 2.40±0.31. Mean age (days) at onset of jaundice in 2 groups were 3.92 ± 2.43 in BA and 6.5 ±4.5 in NH. Most patients of BA (91%) had persistent acholic stool, whereas in Neonatal hepatitis group 83% had intermittent acholic stool. No statistically significant difference was observed when hepatosplenomegaly and ALT values were considered in 2 studied groups. In BA group 33% & In NH group 72% babies had positivity for CMV infection. Normal ultrasonic findings were seen in 2 patients of BA group, and 7 in NH group. No patient had shown contracted gall bladder after meal in BA, Choledocal cyst was found to be responsible for 5 (42%) patients in BA group and none in NH group. HIDA showed 47% had biliary atresia, 43% neonatal hepatitis and 10.0% had normal liver. Liver biopsy reveled that 12 (40.0%) had biliary atresia and 18 (60.0%) had neonatal hepatitis. Out of 12 babies in Biliary atresia group almost all, 11(92%) received surgical management where as in Neonatal hepatitis group; all 18 babies (100%) received medical treatments. Early detection of cholectatic cases by observing stool colour is very important for physicians to direct the very specific investigations to find out the cause and start appropriate treatment immediately.

Key words: Cholestatic Jaundice, Biliary Atresia, Neonatal Hepatitis, Infancy.

Introduction:

Jaundice is caused by elevated serum bilirubin concentration. It is apparent in infants when the serum bilirubin value is greater than 4 to 5 mg/dL (68.4 to 85.5 mcmol/L) and in older children at values greater than 2 to 3 mg/dL (34.2 to 51.3 mmol/L).[1,2] Serum total bilirubin is measured in the laboratory as the sum of two components: unconjugated ("indirect") and conjugated ("direct") fractions. The terms "direct" and conjugated hyperbilirubinemia often are used interchangeably. Conjugated hyperbilirubinemia is defined as a conjugated bilirubin concentration greater than 2 mg/dL (34.2 mmol/L) or more than 20% of total bilirubin. It is the biochemical marker of cholestasis used most commonly and defined as perturbation of bile flow. Conjugated hyperbilirubinemia is less common, affecting approximately 1 in 2,500 infants.[3,4] This condition is never normal at any age, and distinguishing cholestasis from noncholestatic causes of jaundice is crucial. Prolonged hyperbilirubinemia of greater than 2 to 3 weeks duration requires additional investigations.[5]

It is paramount to fractionate the bilirubin in infants who have abnormal or prolonged jaundice to identify those who have conjugated hyperbilirubinemia and recognize the disorders that may be amenable to early medical intervention (eg, galactosemia, urinary tract infection) or surgery (eg, biliary atresia, choledochal cyst).[6] In addition, early diagnosis facilitates the institution of necessary nutritional and medical support to promote optimal growth and development.[7] The consequences of infantile cholestasis are profound, resulting in malabsorption, failure to thrive, and deficiencies of fat-soluble vitamins. Cholestatic babies are at special risk for life-threatening bleeding due to vitamin K deficiency. These babies need more calories to maintain growth and also supplementation of vitamins A, D, E and K at

1. Dr. Farzana Hamid, Asst. Prof of Paediatrics, Delta Medical College, Dhaka.
2. Dr. Ainun Afroza, Prof. & Head, Dept of Paediatric Gastroenterology, BSMMU, Dhaka.
3. Dr. Prokash Chandra Ray, Consultant of Paediatrics, Dhaka Mohanagar Shishu Hospital.

Corresponding Author:
Dr. Farzana Hamid, Asst. Prof of Paediatrics, Delta Medical College, Dhaka.

diagnosis and thereafter.[8] The Children's Liver Disease Foundation launched an educational program in the United Kingdom in 1993 with the help of the Department of Health to improve the outcome of infantile hepatobiliary diseases. The aim of that campaign was to make certain that all babies who remain jaundiced after 2 weeks of age are tested for conjugated hyperbilirubinemia and referred for timely management.[8] Pilot programs have also been developed in Japan and Taiwan, wherein color cards are given to mothers for early recognition of acholic stools.[9] An awareness campaign is urgently required to improve the outcome in Bangladesh and other countries observed to have such a delay in cholestatic babies referral.[2,10]

Materials and Methods:

This Prospective study was conducted in the Department of Pediatric Gastroenterology & Nutrition, Bangabandhu Sheikh Mujib Medical University from July 2007 to December 2007. Ethical clearance was taken from the ethical clearance committee before study. Total thirty patients were enrolled in this study. Sampling technique was non probability purposive sampling. Inclusion criteria of patients were infants (2 weeks to 12 months), both sexes, infants with cholestatic jaundice (S, conjugated bilirubin > 2 mg or more than 20% of total bilirubin) persisting beyond 2 weeks of age. Exclusion criteria of patients were age more than 12 months & less than 2 weeks, jaundice due to other causes, seriously ill infants who need referral. A detailed history was obtained from mother of infants with cholestatic jaundice (scleral icterus, dark urine and pale stool) persisting beyond 2 weeks of age and was recorded in a predesigned questionnaire. A thorough physical examination, including examination of the eyes, stool color were observed daily after admission to look for persistent or intermittent nature of icterus and pale stool and examination findings were recorded. Complete blood count and liver function tests (S. bilirubin - total & direct, ALT, ALP, and PT) were done. Urine was tested for non-glucose reducing substances. Ultrasonography of the hepatobiliary system, Hepatobiliary scintigraphy was done after IV administration of 3 mci of mebrofenin (BrIDA), following 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 considered as absent tracer excretion. Liver biopsy was done in appropriate patients. To find out the causes of neonatal cholestasis, blood examination for HBsAg and TORCH screening, thyroid function test were done. Patients were followed up daily during hospital stay. The management & its response were also monitored and recorded. The short term outcome during hospital stay was noticed. The whole analysis was done with the help of computer using SPSS (Statistical package for social science) program version 10. Continuous variables were summarized as groups or as mean + standard deviation (SD) and categorical data as frequencies and percentages. For continuous variables differences among groups were analyzed by Analysis Of Variance (ANOVA) test. The chi-square test was applied to compare differences between discrete variables. For multiple comparisons a 'p' value <0.05 was considered statistically significant.

Results:

Table 1 showed clinical findings in the studied groups. Most of the patients were male, 10 (83%) in BA, 14 (78%) in NH. Only 2 and 4 were female in BA & NH respectively. Out of 12 patients in BA, 11(92%) were term and only 1 was preterm, whereas in NH group, larger number of babies 10(56%) were preterm and 8 (44%) out of 18 babies were term babies, which was statistically significant ($p<0.05$). Among mothers of NH babies, maternal fever was seen in 5 (28%) subjects and only 2 out of 12 (17%) mothers of BA group gave history of fever. Only 2 mothers in NH had rash and none in BA group. 2 (17%) out of 12 in BA had ascitis and 1 baby had oedema. Similar findings were noticed in NH group too, 2(11.1%) out of 18 had ascitis and 1(5.6%) baby had oedema. Among the patients of biliary atresia out of 12, 11 (91%) had persistent acholic stool and only 1 patient had intermittent acholic stool. Whereas in Neonatal hepatitis group, 15 (83%) out of 18 had intermittent acholic stool and 3 (16%) had persistent acholic stool, which was statistically significant (p value < .05).

Table 1 showed clinical findings in the studied groups.

	Biliary atresia (n=12)	Neonatal hepatitis (n 18)	p value*
Sex			
• Male	10 (83.0)	14 (77.8)	1.00
• Fema le	2 (16.7)	4 (22.2)	
Gestational age			
• Term	11 (91.7)	8 (44.4)	0.025 s
• Preterm	1 (8.3)	10 (55.6)	
Maternal features			
• Fever	2 (16.7)	5 (27.8)	0.792
• Rash	0 (.0)	2 (11.1)	0.654
• Pruritus	1 (8.3)	0 (.0)	0.836
Patient's feature			
• Ascitis	2 (16.7)	2 (11.1)	1.00
• Oedema	1 (8.3)	1 (5.6)	1.00
Acholic stool			
• Persistent	11 (91.7)	3 (16.7)	0.001
• Intermittent	1 (8.3)	15 (83.3)	

Figure within parenthesis denoted corresponding percentage
* Chi square test (after Yates correction) was done to measure the level of significance. P value <0.05 was considered as level of significance.

Table 2 showed clinical & biochemical characteristics of babies with cholestatic jaundice.

	Biliary atresia (n=12) [Mean±SD]	Neonatal hepatitis (n 18) [Mean±SD]	p value*
Age (month)	4.13±2.11	3.86±2.11	0.740
Birth weight (kg)	2.65±.13	2.40±.31	0.013 s
Weight at admission	4.97±1.32	4.42±1.33	0.279
Weight at discharge	4.66±1.37	4.41±1.34	0.631
Age at onset of jaundice (days)	3.92±2.43	6.5±4.55	0.083
Liver enlargement (cm)	4.29±1.63	3.74±1.0	0.264
Splenic enlargement (cm)	1.167±1.27	0.78±1.0	0.357
Liver function test			
Serum bilirubin (total)			
• Day of admission	13.32±3.66	12.05±6.69	0.553
• Day of discharge	21.14±29.77	11.10±6.37	0.174
Serum bilirubin (direct)			
• Day of admission	9.08±2.78	8.28±4.83	0.609
• Day of discharg	8.84±2.68	7.32±4.35	0.292
ALP (IU/L)	266.42±249.38	119.5±59.58	0.022s
ALT (U/L)	129.75±71.02	130.0±78.16	0.993
Serum albumin	33.9±4.07	33.68±2.76	
Thyroid function test			
FT4	9.33±4.89	2.71±1.51	0.475
TSH	10.66±4.97	4.39±2.61	0.054

Table 2 showed clinical & biochemical characteristics of babies with cholestatic jaundice. At presentation, mean age of babies in BA group was 4.13± SD 2.11months, where as in NH babies mean age was 3.86 ± SD 2.11 months. Mean value of birth weight in BA was 2.65±.13 Kg and in NH babies was 2.40±.31 Kg, which was statistically significant (p-0.013s). Mean age (days) at onset of jaundice in 2 groups were as follows- 3.92 ±2.43 in BA and in NH it was 6.5 ±4.5. No statistically significant difference were observed when hepatosplenomegaly were considered in 2 studied groups .Mean value for hepatic enlargement in BA were 4.29±1.63 cm Vs 3.74±1.0 cm in NH group. Mean value for splenic enlargement in BA were 1.167±1.27 cm Vs 0.78±1.0 cm in NH group. Liver function tests in BA babies showed mean value of total serum bilirubin at admission 13.32±3.66 mg/dl Vs 12.05±6.69 mg/dl in NH babies which was not statistically significant (p value- 0.553). At discharge it was 21.14±29.77 mg/dl in BA babies , 11.10±6.37 mg/dl in NH babies, which was again statistically not significant (p value- > 0.05). Direct serum bilirubin in 2 studied groups also showed no statistical significance. Direct serum bilirubin level reveals at D1 9.08±2.78 mg/dl in BA Vs 8.28±4.83 mg/dl in NH with a p value of 0.609, and at discharge, mean values were 8.84±2.68 in BA Vs 7.32±4.35 in NH with a p value of 0.292. ALP showed statistical significant difference with mean value of 266.42±249. 38 in BA Vs 119.5±59.58 (p value- 0.022 s). Mean value for ALT were 129.75±71.02 in BA and 130.0±78.16 in NH babies which was statistically not significant.

Table 3 showed TORCH screening & USG finding of babies with cholestatic jaundice. Among biliary atresia group, 4 (33%) were found to be positive for CMV infection, and only 1 baby was positive for HSV infection. In NH group, 13(72%) babies had positivity for CMV infection and 5 (28%) for HSV infections, which was statistically significant (p value < .05). Out of 30 patients, normal ultrasonic findings came out in 2 (17%) patients of biliary atresia group, and 7 (39%) in NH group. 10 (55%) patients of NH and 5 (42%) patients of BA had shown contracted gall bladder both before and after meal. On the other hand no patient had shown contracted gall bladder after meal in BA, 1 baby among NH showed contracted gall bladder after meal. Choledochal cyst was found in 5 (41.7%) patients of BA group.

Table 3 showed TORCH screening & USG finding of babies with cholestatic jaundice.

		Biliary atresia (n=12)	Neonatal hepatitis (n 18)	p value*
TORCH Screening				
	CMV	4(33.3)	13 (72.2)	0.035*
	HSV	1 (8.3)	5 (27.8)	0.403**
USG finding	Normal	2 (16.7)	7 (38.9)	0.022
	Contracted gall bladder before and after meal	5 (41.7)	10 (55.6)	
	Contracted GB after meal	0(.0)	1 (5.6)	
	Choledocal cyst	5(41.7)	0(.0)	

Table 4 showed HIDA findings in Cholestatic Jaundice. Out of 30 patients, 14 (46.7%) had biliary atresia, 13 (43.3%) had neonatal hepatitis and 3 (10.0%) had normal liver by HIDA.

	Frequency	Percent
Biliary atresia	14	46.7
Neonatal hepatitis	13	43.3
Normal	3	10.0

Table 5 showed liver biopsy finding in Cholestatic Jaundice. Out of 30 patients 12 (40.0%) had biliary atresia and 18 (60.0%) had neonatal hepatitis.

	Frequency	Percent
Biliary atresia	12	40.0
Neonatal hep atitis	18	60.0
Total	30	100.0

Table 6 showed comparisons of treatments in Cholestatic babies. Out of 12 babies in Biliary atresia group almost all, 11(92%) received surgical management where as in Neonatal hepatitis group; all 18 babies (100%) received medical treatments.

Management	Group		p value*
	Biliary atresia (n=12)	Neonatal hepatitis (n 18)	
Medical	1 (8.3)	18 (100.0)	0.001
Surgical	11 (91.7)	0 (.0)	
Total	12 (100.0)	18 (100.0)	

Discussion:

In our study, at presentation, mean age of babies in BA group was 4.13± 2.11SD, where as in NH babies mean age was 3.86 ± 2.11SD. Mean age at onset of jaundice in 2 groups were 3.92 ±2.43 in BA and in NH it was 6.5 ±4.5. In infants with BA, delay in presentation and diagnosis is the single most important factor that results in poor prognosis in developing countries.[1,2] The mean age at presentation to hospital of BA cases in the series by Karim B et al was 3.5 months,[2] though the mean age of onset of jaundice was[5]. 8 days. Matthai J et al 7 reported the mean age at presentation to hospital in their series was 2.9 months, while the mean age at onset of jaundice was 40 days. Yachha et al 5 also reported considerable delay (mean [SD] 4 months in BA, and 2.2 months in NH) in presentation to hospital. Biliary atresia has been reported to be commoner in female infants.[11] We found most of the patients were male, 10 (83%) in BA, 14 (78%) in NH. Only 2 and 4 were female in BA & NH respectively in our study. However, in Karim et al series, 10 of 16 infants with BA were male. 2 Crofts DJ et al showed that Infants with neonatal hepatitis were found to have low birth weight and later onset of jaundice than those having biliary atresia.[12] In the present study, it was found that mean value of birth weight in BA was 2.65±.[13] and in NH babies it was 2.40±.31, which is statistically significant (p-0.013).

CMV infection was found to be the commonest cause of neonatal hepatitis.[13] Dick et al[14] suggested idiopathic hepatitis as the main cause of neonatal hepatitis, but their studies antedate the descriptions of recently recognized metabolic causes of cholestasis. On the other hand, advances in preventive medicine may result in the lower incidence of congenital infections compared to idiopathic hepatitis in some recent studies.[15] In our study among biliary atresia group, 4 (33%) were found to be positive for CMV infection, and only 1 baby was positive for HSV infection. In NH group, 13(72%) babies had positivity for CMV infection and 5 (28%) for HSV infections, which was statistically significant (p value <.05). Persistent acholic stools are an important feature of BA.[12,15] In the study by Karim et al, 13 of 16 infants with BA and 16 of 37 infants with NH/INH had such stools. In BA, during the initial phase of the illness, stools may contain some bile pigment and may not be totally acholic. In that series, intermittent pale-colored stools were observed in 3 of 16 BA cases.[2,15] In our study, out of 12 patients of Biliary atresia 11 (91%) had persistent acholic stool and only 1 patient had intermittent acholic stool. Whereas in Neonatal hepatitis group, 15 (83%) out of 18 had intermittent acholic stool and 3 (16%) had persistent acholic stool, which is statistically significant (p value <.05). Splenomegaly was found in higher percentage in infants with neonatal hepatitis compared to biliary atresia cases.[16] In contrast, no statistically significant difference was observed when hepatosplenomegaly was compared in 2 studied groups. Mean value for hepatic enlargement in BA were 4.29±1.63 Vs 3.74±1.0 in NH group. Mean value for splenic enlargement in BA were 1.167±1.27 Vs 0.78±1.0 in NH group in present study.

It is difficult to differentiate BA from other causes of cholestasis by biochemical tests.[15,16] It has been reported that serum bilirubin rarely exceeds 12 mg/dL (and may be as low as 5-8 mg/dL) in infants with BA despite complete bile duct obstruction, whereas it may exceed 20 mg/dL in those with NH.[11,15] In the series by Karim et all, mean serum bilirubin was 10.4 mg/dL in infants with BA and 14.1 mg/dL in those with NH.[2] In our study, we found liver fuction tests in BA babies showed mean value of total serum bilirubin at D1 13.32±3.66 Vs 12.05±6.69 in two groups which is not statistically significant (p value-0.553). At discharge it was 21.14±29.77 in BA babies,

11.10±6.37 in NH babies , which is again statistically not significant (p value- > 0.05). Direct serum bilirubin in 2 studied groups also showed no statistical significance. At D1 it was 9.08±2.78 in BA and 8.28±4.83 in NH with a p value of 0.609, and during discharge , mean values were 8.84±2.68 in BA Vs 7.32±4.35 in NH with a p value of 0.292. ALP showed statistically significant difference with mean value of 266.42±249.38 in BA Vs 119.5±59.58 in NH group (p value- 0.022s). Mean value for ALT was 129.75±71.02 in BA and 130.0±78.[16] in NH babies, which were also not statistically significant. Serum GGT level is the only biochemical test found to be of discriminating value.[15] GGT values less than 200 U/L correlated with the diagnosis of hepatocellular cholestasis while GGT values more than 200 U/L favored the diagnosis of biliary atresia. However, low or normal GGT level was found in patients with Byler's disease and benign recurrent intrahepatic cholestasis.[14] We did not consider GGT values in the current study. Abdominal ultrasonography is an important investigation in the diagnosis of cholestatic disorders.16 Visualization of a normal gall bladder while fasting and contraction after meal virtually rules out BA, but the reverse is not always true.[17] In the current series, out of 30 patients, normal ultrasonic findings detected in 2 (17%) patients of BA group, and 7 (39%) in NH group. 10 (55%) patients of NH and 5 (42%) patients of BA had shown contracted gall bladder before and after meal respectively. On the other hand no patient had shown contracted gall bladder after meal in BA, but it was found in 1 baby with NH. Choledochal cyst was detected in 5 (41.7%) patients of BA group. Another important investigation is hepatobiliary scintigraphy, using 99mtechnetium iminodiacetic acid derivatives.[18] Out of all patients of our study group, 14 (46.7%) had biliary atresia, 13 (43.3%) had neonatal hepatitis and 3 (10.0%) had normal liver as diagnosed by HIDA. The most accurate test for differentiating BA from other conditions is percutaneous liver biopsy, which has a diagnostic accuracy of 90% to 95% for BA.[19]. Karim et al showed typical features of BA in 6 of 10 cases and features of early biliary cirrhosis in 4 infants. Late presentation may have been responsible for a high frequency of cirrhosis in their cases.[20] In our study, liver biopsy reveled that 12 (40.0%) had biliary atresia and 18 (60.0%) had neonatal hepatitis Out of 12 babies in Biliary atresia group almost all, 11(92%) received surgical management where as in Neonatal hepatitis group; all 18 babies (100%) received medical treatments. Two recent studies[19,21] reported biliary atresia in 34% and 19.4% of infants with cholestatic syndrome respectively. Chardot C et al had shown early diagnosis and surgical correction is of most benefit for such patients.[22]

Conclusion:

The management protocol of cholestatic jaundice in developing countries should be cost-effective, quick and appropriate for a given clinical setting.[2,21] Observing stool color on three consecutive days by the doctor is mandatory. This step helps in prioritizing the direction of investigations. Passage of yellow stools after 4 weeks of age almost rules out the possibility of EHBA. Babies with cholestatic jaundice, looking sick (refusal of feeds, irritability, fever, altered sensorium, coagulopathy, abdominal distension, etc.) should be managed promptly,[21,22] as these babies are likely to have galactosemia, intrauterine infections, tyrosinemia and congenital hemochromatosis. Babies not looking sick and passing pale stools should undergo ultrasonography to rule out choledochal cyst followed by liver biopsy to diagnose EHBA. In summary, there is urgent need to create greater awareness about cholestasis where referral is delayed.[23] This effort will salvage a number of infants and may help reduce the infant mortality rates. Introduction of a cheap and easy method like colour card at community level may help early detection of cholestatic cases.[23]

Study limitation:

Number of study population was limited and Gamma GT, Alpha 1 antitrypsin level, Hepatitis C virus could not be done due to financial constraint of parents.

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