



Original Research Article

Clinic-o-etiological profile of cholestasis in infants in a tertiary care center

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ABSTRACT

Introduction: Common presenting feature of hepatobiliary and metabolic dysfunction in neonates is cholestatic jaundice. It is essential to recognise the neonatal cholestasis early. Significant proportion of cases of cholestatic disease are constituted by EHBA. If management of Extra Hepatic Biliary Atresia is delayed beyond three months of life, only option available then is liver transplantation.

Aim: To analyse etiological factors and to study clinical presentation of cases presenting with cholestasis.

Objectives: Study the clinical presentation and analyse the etiological factors in infants with cholestasis. To determine the validity of ACS and compare outcomes of EHBA with respect to age at presentation.

Materials and Methods: Prospective observational study was done in 104 infants with cholestasis who were admitted in Paediatric ward of Niloufer hospital from January 2019 to July 2020.

Statistical analysis done by chi square test and Fisher's exact tests.

Results: Of the total 104 cases, 47 cases were diagnosed to be EHBA and 38 cases were found to have neonatal hepatitis. 58.6% were male and 41.34% were female and 72 were term and 32 were preterm. Mean age of presentation with EHBA and Neonatal hepatitis was 91 days and 94 days. LFT's in EHBA cases showed mean TSB 12.19 ± 5 mg/dl Vs 11.7 ± 5.8 mg/dl in NH babies with a p value equal to 0.379. Direct bilirubin revealed 6.44 ± 3.1 mg/dl Vs 6.64 ± 3.1 mg/dl in NH group ($p = 0.824$). HIDA scan showed 41% had EHBA, 33.3% had NH.

Conclusion: AIIMS Clinical score (ACS) cannot correctly differentiate EHBA from NH.

Survival was significantly higher in infants with EHBA who were operated before 60 days of life.

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1. Introduction

Common presenting feature of hepatobiliary and metabolic dysfunction in infants is cholestatic jaundice. During the first 2 weeks of life,¹ jaundice is the common clinical finding. Most often, of the indirect bilirubin variety and usually resolves spontaneously without any intervention. However, persistent jaundice and jaundice of direct bilirubin variety is abnormal and can be a sign of serious hepatobiliary and metabolic dysfunction.

In babies with persistent jaundice i.e beyond 2 weeks of life, conjugated hyperbilirubinemia must be considered in the differential diagnosis and should be evaluated for cholestasis. If cholestasis is present then early identification of the cause should be done by directing specific investigations.

Infants with cholestasis benefit from medical management if given early even when specific treatment is not available. Optimization of nutrition is important to prevent complications. Despite studies showing that early diagnosis of cholestasis is life-saving, delayed diagnosis due to late referrals remains problem in India.² Causes of

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late referrals include early hospital discharge of neonates, inadequate follow-up of cases with persisting jaundice, false reassurance due to appearance of pigmented stools, fluctuating levels of serum bilirubin, and misdiagnosis of human milk associated jaundice.^{3–5}

2. Aim

To analyse etiological factors and to study clinical presentation of cases presenting with cholestasis

3. Objectives

1. To study clinical profile of cholestasis in infants.
2. Analyse etiological factors of cholestasis in infants.
3. To determine the validity of Aims Clinical Score (ACS).
4. To compare outcomes of extra hepatic biliary atresia in infants with respect to age at presentation.

4. Materials and Methods

A prospective observational study was done in 104 infants with cholestasis who were admitted in Pediatric ward of Niloufer hospital from January 2019 to July 2020

Approval from Institutional ethical committee was taken before the commencement of the study. After taking informed consent infants in the age group of 2 weeks to 12 months, admitted to Pediatric ward of Niloufer hospital with Serum conjugated bilirubin > 20% Of total bilirubin and >2mg/dl persisting beyond 2 weeks of age were screened and 104 infants who satisfied the criteria were included in the study. Infants with bacterial or fungal sepsis, Primary hemolytic disease, Drug or TPN associated cholestasis and severely ill infants were excluded from the study. Clinical profile, ultra-sonogram, hepato-biliary scintigraphy (HIDA), liver biopsy, LFT, routine blood tests and other relevant investigations were studied. Data was entered in a pre designed proforma. Statistical analysis of the data was done by Statistical Package for Social Sciences (SPSS) 19.0. Data presented as tables, bar charts, pie charts. Association between variables was studied using chi square test and fisher's exact tests of statistical significance. 2 tailed P values have been calculated. A 2 tailed P value < 0.05 is considered statistically significant.

5. Results

Out of total 104 cases presented to pediatric ward during the study period with cholestasis 47 (45.1%) cases were found to have extra hepatic biliary atresia and 38 (36.5%) cases were found to have neonatal hepatitis (figure 1).

Of the 104 cases 61 (58.6%) were male and (41.34%) were female and 72 (69.2%) were term and 32 (30.7%) were preterm. In infants with cholestasis, 48% of the total cases presented before 2 months of age. In our study group,

most common presenting clinical features were jaundice, pale colours stools, high colours urine and organomegaly. In our study group, 16.3% of the total cases with cholestasis had history of maternal fever. 11% of the total cases had hearing impairment, 28% cases had microcephaly and 20% cases were born with IUGR.

Table 1 showed clinical biochemical findings in the studied groups.

In both the groups Male infants were affected more when compared to female infants. Out of 47 cases of EHBA 36 (76.5%) were term and 11 (23.4%) were female. Out of 38 cases of neonatal hepatitis 50% were preterm. Mean age of presentation with EHBA and Neonatal hepatitis was 91.3 days and 94.1 days. Age at onset of jaundice were 8.4 days in EHBA and 48 days in NH group. History of maternal fever showed no difference when compared among both groups (p value 0.866). Persistent clay coloured stools were more common in EHBA babies (74.2% of total EHBA cases) when compared to intermittent clay coloured stools in neonatal hepatitis (84.2% of total NH cases) group. No statistical significance was observed when HSM (hepatosplenomegaly) was considered in both the groups (p value = 0.059).

Liver Function Tests (LFT's) in EHBA group showed mean TSB 12.19 ± 5 mg/dl Vs 11.7 ± 5.8 mg/dl in NH group which was not statistically significant (p value = 0.379). Direct bilirubin in 2 studied groups showed no statistical significance. Direct serum bilirubin level showed 6.62 ± 3 mg/dl in BA Vs 6.44 ± 3.1 mg/dl in NH with a p value = 0.824. ALP showed no statistical significance with mean value 702.4 ± 312.3 in BA Vs 522.3 ± 451.9 (p value = 0.488). Mean value for SGOT were 323.6 ± 377 in BA and 432 ± 506 in NH babies showed no statistical significance.

Table 2 showed evaluation of ultra-Sonogram findings of gallbladder in infants with cholestasis.

In our study, abnormal gall bladder findings in infants with Extra Hepatic Biliary Atresia and Neonatal hepatitis (NH) were compared. Usefulness of ultrasonography was determined in differentiating EHBA from Neonatal hepatitis. Infants with both Extra Hepatic Biliary Atresia and Hepatitis were excluded. An abnormal gall bladder findings were noticed in 27 of 41 EHBA cases, thus giving a sensitivity of 65.85%. Normal gall bladder findings were observed in 29 of 37 NH cases giving a specificity of 78.38%. Out of total 35 cases with abnormal gall bladder findings, 27 had giving Extra Hepatic Biliary Atresia, giving a positive predictive value of 77.1%. 29 of 43 cases with NH had a normal gall bladder findings, thus giving a negative predictive value of 67.4%. In 56 infants out of total 78 cholestatic cases, the gall bladder findings were correlated with final diagnosis, giving diagnostic accuracy of 71.7%.

Another important investigation is hepatobiliary scintigraphy which helps in differentiating EHBA from Neonatal Hepatitis. In this study sensitivity, specificity,

positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy of HIDA scan was 78.05%, 29.73%, 55.17%, 55% and 55.13%. (Table 3)

AIIMS clinical score (ACS) was ≥ 10 in 30 children (38.4%), was < 10 in 48 children (61.5%). Of the 41 infants diagnosed to have Extra Hepatic Biliary Atresia 32 infants had a score < 10 , giving a sensitivity of 78.05%. of the 37 children diagnosed as Neonatal Hepatitis (NH) 21 infants had a score ≥ 10 , giving a specificity of 56.76%. Among the 48 children who had ACS of < 10 , 32 infants were Extra Hepatic Biliary Atresia thus giving a PPV of 66.67%. Among the children who had ACS of 10 or more, 21 infants were diagnosed to have NH thus giving a NPV of 70%. The diagnostic accuracy of this ACS 67.95%. (Table 4).

During the study period, 40 cases of EHBA out of total 47 cases were followed up for 6 months and 35 cases were taken up for the study, 5 cases were lost to follow up. Outcomes were assessed with respect to age at presentation. Out of 35 cases, 18 (51.5%) cases came to our hospital for the first time beyond 60 days of life where as 17 patients (48.5%) came to hospital before 60 days of life. 5 cases were deferred surgery due to delayed presentation (beyond 5 months) to the hospital. Mean age at presentation to hospital was 77 Days of life. Mean age when jaundice was noticed by parents was 8 Days of life. Mean age of clay coloured stools noticed by parents was 17 Days of life.

Outcomes when assessed Survival rate (at one year) in infants with EHBA when operated by Kasai Portoenterostomy before 2 months of life was significantly higher (94.1%) when compared to infants who were operated beyond 2 months of life (46.1%) which was statistically significant (by Fishers exact test) with a p value 0.0094. (Table 5)

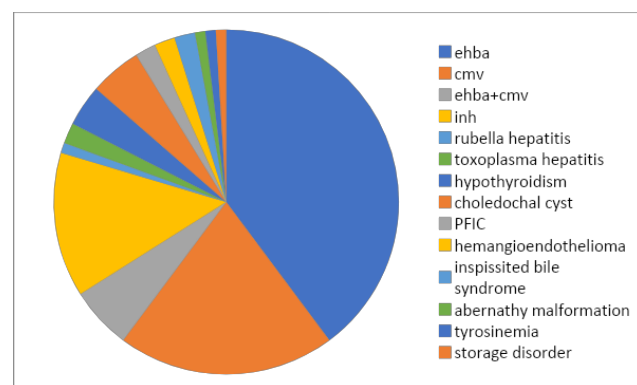


Figure 1:

6. Discussion

This study was undertaken to analyse etiological factors, to study clinical profile, to validate AIIMS Clinical Score

and to assess outcomes with respect to age at surgery (Kasai portoenterostomy).

Globally, the causes of cholestasis in infancy are obstructive causes (like Extra Hepatic Biliary Atresia and choledochal cysts), hepatocellular causes (like infections, metabolic, miscellaneous, unknown etiology) and paucity of bile ducts. Hepatocellular causes constitute 45% to 69% while obstructive causes account for 19% to 55% of all cases.¹³

In our study, analysis of results revealed EHBA was major etiology among all other groups, contributing to 39% of total study population, remaining were neonatal hepatitis (28.2%), INH (13.5%), both EHBA and NH (4.8%) and others (17%).

Table 6 Showed Results from our study were comparable with other studies i.e most common etiologies for cholestasis in infants were EHBA followed by Neonatal hepatitis.

Table 7 Showed comparison of clinical characteristics with other studies. Mean age at presentation in group Extra Hepatic Biliary Atresia was 91.3 days, where as Neonatal Hepatitis babies mean age was 94.1 days. We found most of the patients were male 71% in NH and 57% in EHBA and preterm babies were more in NH group where as term babies were more in EHBA group

Major studies done in India reported mean age of presentation to be around 3.5 months. The male to female ratio in these studies was similar to our patient group. The late presentation in our study may be due to mild nature of jaundice, health care providers incorrectly diagnosing as breast milk jaundice and late referral from peripheries.

The presenting clinical features in our patients were jaundice, pale stools, high coloured urine and organomegaly. In the study done by mayank et al, most common presenting clinical features were jaundice, failure to thrive and organomegaly.⁷ Ahmed et al¹⁴ reported jaundice, listlessness, organomegaly and failure to thrive as the main clinical presentation. However, we found failure to thrive to be less common in our group.

Differentiating EHBA from other causes of cholestasis by biochemical tests¹¹ is difficult. Total serum bilirubin rarely exceeds 12mg/dl in infants with biliary atresia even with complete obstruction of bile duct, where as it may exceed 20mg/dl in those with Neonatal Hepatitis.⁸

In the study done by karim et al,⁹ mean Total serum bilirubin was 10.4 mg/dl in Extra Hepatic Biliary Atresia babies and 14.1mg/dl in those with NH group. In our study, mean total serum bilirubin value was 12.1 ± 5 in infants with EHBA and 11.7 ± 5.8 in those with NH with p value = 0.379 which was not statistically significant. Direct bilirubin when studied in two groups also showed no significance statistically. Serum ALP values also showed no statistical significance.

Table 1: Clinical and biochemical parameters were compared among EHBA group and Neonatal Hepatitis group

	EHBA	NH	P value
Age at presentation	3 months	3 months	0.404
Age at onset of jaundice(days)	8.4±11.4	48.7±82.8	0.000
Birth weight(kg)	2.58±0.51	2.25±0.69	0.047
Sex			0.195
Male	27	27	
Female	20	11	
Gestational age			0.01
Term	36	19	
Preterm	11	19	
Maternal fever	8	7	0.866
Stool			0.00
Persistent	74.2%	25.8%	
Intermittent	15.8%	84.2%	
High coloured urine	62.7%	37.3%	0.038
Firm liver	65.9%	34.1%	0.059
TSB	12.19±5	11.7±5.8	0.379
Direct	6.62±3	6.4±3.1	0.824
Indirect	5.52±2.9	5.33±3.2	0.598
SGOT	207.26±311.4	202.4±217.2	0.383
SGPT	323±377.8	432.05±506.3	0.842
ALP	702.4±312.3	522.3±451.9	0.488

Table 2: Evaluation of gall bladder findings in infants with cholestasis

Gall bladder findings	EHBA	NH	Total
abnormal	27	8	35
Normal	14	29	43
Total	41	37	78

Table 3: Evaluation of HIDA scan in infants with cholestasis

HIDA	EHBA	NH	Total
Positive	32	26	58
Negative	9	11	20
Total	41	37	78

Table 4: Evaluation of AIIMS clinical score

ACS	EHBA	NH	Total
<10	32	16	48
>10	9	21	30
Total	41	37	78

Table 5: Outcome after kasai procedure in relation to timing of surgery before two months and after two months

Age (In months)	Kasai operation	Survival at 1 year of age
< 2 months	17 (48.5%)	16 ((94.1%)
>2 months	13 (51.5%)	6 (46.1%)

Statistical analysis by Fishers exact test p value = 0.0094

Table 6: Comparison of etiological factors in various studies

Study	EHBA	NH	INH	OTHERS
Our study	39	28.2	13.5	17
rinku meena et al ⁶	30	28		
Mayank jain et al ⁷	41	20	18	21
Fr chowdhury et al ⁸	42.5	20	25	12.5
Karim et al ⁹	25.8	35.5	24.2	14
Yacha et al ¹⁰	55	11.6	11	21

Table 7: Comparison of clinical characteristics in various studies

Clinical feature	Our study	Karim et al ⁹	Yacchha et al ¹⁰	Chowdhari et al ⁸	Hamid et al ¹¹
Age at presentation					
NH	3months	3.5month	2.8 ±1.3	105.05±16.8	3.8±2.1
EHBA	3months	3.5month	4.4±1.9	113.7±15.3	4.1±2.1
Mean age at onset of jaundice					
NH	48.7	20.8days	16.6±12.7	12.4±4.7	6.5±4.5
EHBA	8.4	5.8days	12.6±9.5	10.1±4.1	3.9±2.4
Persistent acholic stool					
NH	25.8	43.2%	50%		16.7%
EHBA	74.2	81.3%	100%	88.2%	91.7%
Intermittent acholic stool					
NH	84.2	32.4%		77.7%	83.3%
EHBA	15.8	18.8%			8.3%
hepatomegaly					
NH	94.5%	86.5%	100%	88.2%	
EHBA	95.7%	87.5%	100%	77.7%	
splenomegaly					
NH	86.4%	73%	94%		
EHBA	85.1%	62.5%	97%		

Table 8: Comparison of Outcomes of EHBA with other studies

	Our study	Sujay choudhari et al ¹²
Cases	35	26
Duration of study	1 year	5 year
Mean age	77 days of life	1month to 9 month
Mean age of jaundice	8 days of life	1 to 21
Male: Female	1:1	2.2:1
Term: Preterm	3.5:1	24:1
Kasai procedure		
<2months	42%	34%
>2months	58%	66%
Survival at 1 year		
<2months	94.1%	100%
>2months	46.1%	Nil

In the study done by F Hamid et al,¹¹ biochemical characteristics when analysed between NH group and EHBA group showed no statistical significance except for GGT which was comparable with our study.

Abdominal USG is one of the important investigations in diagnosis of cholestatic disorders. Gall bladder visualisation while fasting and contraction of gall bladder after meals virtually rules out biliary atresia, but reverse is not always true.¹⁵

In our study gall bladder was not visualised in 32(80%) cases in EHBA group when compared to 8(20%) cases in those with Neonatal Hepatitis with a statistically significant p value of 0.004. Sensitivity, Specificity, PPV, NPV and overall diagnostic accuracy of ultrasonographically detected abnormal gall bladder findings in differentiating Extra Hepatic Biliary Atresia from neonatal hepatitis was 65.85%, 78.38%, 77.14%, 67.44% and 71.79%.

In one study¹⁶ usefulness of abnormal gall bladder was evaluated. In that study, the Sensitivity, Specificity, PPV, NPV, and overall diagnostic accuracy of abnormal gall bladder findings in diagnosing EHBA from neonatal hepatitis was 71%, 69%, 72%, 69%, and 71%.

Another important investigation is HIDA, using technetium-99m iminodiacetic acid derivatives. Our study showed sensitivity, specificity, PPV, NPV and overall diagnostic accuracy of HIDA scan in differentiating EHBA from NH was 78.05%, 29.73%, 55.17%, 55% and 55.13%. In study done by Daniel K et al,¹⁷ sensitivity of HIDA scan was 100% and specificity was 20% which was comparable with our study.

The triangular cord sign and abnormal gall bladder findings are better than ACS in differentiating EHBA from NH which showed a sensitivity, specificity, PPV, NPV, and overall diagnostic accuracy of 78.05%, 56.76%, 66.6%, 70% and 67.9% respectively.

One study done in India¹⁸ assessed the usefulness of AIIMS clinical score (ACS). In that study sensitivity, specificity, positive predictive value, negative predictive value and the diagnostic accuracy was 91.5%, 76.3%, 89.2%, 80.5%, and 86.6% respectively. Our study showed sensitivity, specificity, PPV, NPV 78.05%, 56.76%, 66.67% and 70% respectively. Overall diagnostic accuracy was 67.95%. Firm liver was given a score of 4 in ACS which was present in both Extra Hepatic Biliary Atresia and NH group. Thus clinical diagnosis alone with AIIMS clinical score was not always correct.

During the study period, 40 cases of EHBA out of total 47 cases were followed up for 6 months and 35 cases were taken up for the study, 5 cases were lost to followup. Outcomes were assessed with respect to age at presentation.

When we compared our study with the study done in PGI Chandigarh there is difference in the gestational preponderance, outcomes of Kasai procedure with respect to age at presentation were comparable in both studies. (Table 8)

7. Conclusion

Most common presenting clinical features in infants with cholestasis were jaundice, acholic stools, high coloured urine and organomegaly. Extra Hepatic Biliary atresia was found to be most common cause in infants with cholestasis followed by Neonatal hepatitis/ Idiopathic Neonatal Hepatitis. AIIMS Clinical score (ACS) cannot correctly differentiate EHBA from NH. Survival was significantly higher in infants with EHBA who were operated before 60 days of life when compared to the infants who were operated beyond 60 days. Early detection of cholestasis done by observing stool colour is very important to direct the specific investigations and to find out the cause. Early medical management and nutritional support improves the outcome of infants with cholestasis.

8. Conflict of Interest

The authors do not have any conflicts of interest.

9. Source of Funding

None.

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