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CLINICAL AND AETIOLOGICAL PROFILE OF INFANTS WITH CONJUGATED HYPERBILIRUBINEMIA IN A TERTIARY CARE CENTER

Paediatrics

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ABSTRACT

Aim: The aim of this study is to find-out the clinical and aetiological profile in infants less than six months and more than 14 days old in a tertiary care cantre in north zone of india.

Patients and methods: This observational study was conducted in the Paediatric Department, SPMCHI, attach to S.M.S. Medical College,Jaipur, Rajasthan over a period of 1 year. 70 cases of cholestatic jaundice were included who fulfilled the inclusion criteria after taking informed written consent.

Results: There were 35 males (50%) and 35 females (50) with a mean age of 84.09 days (range15-180 days). The most common clinical finding was jaundice that was seen in all patients (100%) followed by pale stool in 46 (65.71%), abdominal distension in 40 (57.14%), hepatomegaly in 39 patients (55.71%), dark urine in 26 (37.14%), and splenomegaly in 21 patients (30%). In this study, the most common causes of cholestasis were biliary atresia (21=30%), neonatal hepatitis (20= 28.57%).

Conclusion: The results of this study showed that biliary atresia and neonatal hepatitis are the most common causes of infantile cholestasis in this area.

KEYWORDS

Prospective observational study, Neonatal cholestasis, Biliary atresia

INTRODUCTION:

Neonatal cholestasis syndrome is defined as prolonged elevation of serum levels of conjugated bilirubin beyond the first 14 days of life.According to NASPGHAN, Conjugated hyperbilirubinaemia in a neonate defined as: Direct bilirubin concentration>1.0 mg/dl if TSB<5 mg/dl or Direct bilirubin concentration >20% of TSB if TSB>5 mg/dl. IAP defined Neonatal cholestasis syndrome if conjugated hyperbilirubinaemia>1.5-2 mg% in a newborn/ infant with passage of high coloured urine with or without acholic stools. It is an abnormal finding and requires additional evaluation if it persist beyond 2 weeks of life[1].

An infant with cholestatic jaundice usually presents with prolonged jaundice, pale stool and dark urine. Acholic stool, a cardinal feature of cholestasis should be promptly evaluated. Other clinical features depend on etiology of cholestasis. Cholestatic jaundice in infancy affects approximately 1 in every 2500 term infants and is infrequently recognized by primary providers in the setting of physiologic jaundice.

Any infant noted to be jaundiced after 2 weeks of age be evaluated for cholestasis with measurement of total and direct serum bilirubin, and that an elevated serum direct bilirubin level (direct bilirubin levels >1.0 mg/dl) warrants timely consideration for evaluation. In general, if 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[2]. The success rate for establishing good bile flow after the Kasai operation is much higher (90%) if performed before 8 weeks of life[3].

Nowadays, development of sophisticated diagnostic modalities and methods makes the diagnosis possible in early stages and the underlying cause could be easily discerned. In spite of this, unfortunately there are limited data about the disease among Indian infants.

OBJECTIVE OF STUDY:

To determine common clinical presentations,common aetiological factors, the average age at presentation of infants with cholestasis in infants less than six months old who presented to SPMCHI, S.M.S. Hospital.

METHODOLOGY:

Study site & duration:

This hospital based observational study was conducted at the Department of Paediatric medicine, SPMCHI, attached to S.M.S. Medical College, Jaipur, Rajasthan over one year period.

Study population:

Infants admitted in department of pediatric medicine, SPMCHIand more than 14 days and below 6 months of age who fulfilled the inclusion criteria were included in the study after informed consent.

Inclusion Criteria:

1. All infants >14 days and < 6 month of age presenting with jaundice.
2. Intermittent or persistant pale coloured stool.
3. Passage of dark urine.
4. Conjugated bilirubin concentration (>1.0 mg/dl if TSB<5 mg/dl and >20% of TSB if TSB>5.0 mg/dl).
5. Patient who give consent for the study.

Exclusion Criteria:

1. Neonate or Infant less than 14 days and >6 months of age.
2. Patient of Haemolytic Jaundice.
3. Patients who refuse to give consent for the study.

First line investigations done were complete hemogram, peripheral blood film, detailed liver function test (total and direct bilirubin, SGOT, SGPT, serum alkaline phosphatase, GGT, PT, PT/INR), total protein, serum albumin, renal function tests, blood culture and sensitivity, urine routine microscopy and culture sensitivity, CRP and USG abdomen.

Second line investigations done were FT4, TSH, TORCH profile, HBsAg, HIV, Hepatitis B & C, total galactose, arterial blood gas analysis, serum lactate and ammonia levels.

Other investigations done were MRCP, HIDA scan, Liver biopsy, plasma amino acids and acyl carnitine levels depending upon the initial reports.

Data were collected using a preformed data collection sheet (questionnaire). Statistical analysis was done using the statistical package for social sciences (SPSS version 17.0 for Windows, SPSS Inc. Chicago, IL). All the values were expressed as Mean ± SD; Students unpaired t test were applied as statistical tools. p value of < 0.05 was considered as significance.

RESULTS:

Table 1: Observations of study

S.NO.	CHARACTERISTISC	DATA
1.	Total Infant	70
2.	Gender - Male Female	35 (50%) 35 (50%)

3.	Sex ratio	1:1
4.	Gestational age – Term baby Pre term baby	46 (65.71%) 24 (34.29%)
5.	Birth weight – Range	1000g- 3500g
6	Presentation profile: Age of presentation Age of onset of symptoms Duration of symptoms	84.09 (15 to 180days) 59.70 (since birth to 150days) 41.87 (3 to 180days)

The study showed that there was a significant delay in the presentation of cases of cholestasis to Sir padampat mother and child institute attached to S.M.S. Medical college, Jaipur.The average age of presentation being 84.09 days. Infants who were diagnosed as biliary atresia and neonatal hepatitis presented at the mean age of 83.04 days and 85.1 days. Cases of biliary atresia was referred to paediatric surgery department for kasai procedure hence one of the limitations of this study is lack of Patients survival reviews.

The frequencies of common clinical features for cholestasis in study population are shown in **table 2.**

Table 2: frequencies of common clinical features for cholestasis in study population

		Number of Cases	Percentage
Symptoms	Jaundice	70	100.00
	Dark Urine	26	37.14
	Pale stool	46	65.71
	Abdominal distension	40	57.14
Sign	Hepatomegaly	39	55.71
	Splenomegaly	21	30.00

The frequencies of different etiologies for cholestasis in the study population are shown in **table 3.**

Table 3: Frequencies of different etiologies for cholestasis in study population

	Number of Cases	Percentage (%)
EHBA	21	30.00
Neonatal hepatitis 1.CMV 2.Rubella 3.Viral hepatitis 4.HSV	20 17 1 1 1	28.57 85 5 5 5
Multifactoral 1.CMV+EHBA 2.CMV+Sepsis 3.CMV+Hypothyroidism 4.Sepsis+Hepatitis 5.Sepsis+Choledocal cyst 6.Hepatitis+EHBA	11 6 1 1 1 1 1	15.71 54.55 9.09 9.09 9.09 9.09 9.09
INHS	7	10
Choledhocal cyst	7	10
Sepsis	2	2.85
A1ATD	1	1.42
Endocrinal abnormality	1	1.42
Alagille syndrome	-	-
Cystic fibrosis	-	-
PFIC	-	-
Total	70	100

Twenty of the 70 cases of neonatal hepatitis syndrome, had positive TORCH screening.Most common cause of neonatal hepatitis was cytomegalovirus infection in 17 cases, out of 20 cases. Six patient with biliary atresia co-existed with cytomegalovirus (CMV) infection and three of the cases with sepsis also had cytomegalovirus infection, hepatitis infection and choledocal cyst. one case of cytomegalovirus infection co-existed with hypothyroidism and one case of viral hepatitis accompanied with biliary atresia. The liver biopsies were negative for suspected progressive familial intrahepatic cholestasis (PFIC).

Among the five septic infants all survived. Out of three CMV infection co-existed with other cause, one showed progression of liver disease. However, two cases improved spontaneously.

DISCUSSION:

This was a hospital based prospective observational study, conducted between June 2018 to June 2019 in Department of Paediatric Medicine, SMS Medical College, Jaipur and attached group of hospitals. Our study focussed on finding out clinical and aetiological profile of conjugated hyperbilirubinaemia in infants in a tertiary care centre.

This study showed that the stools of all infants who were eventually diagnosed as biliary atresia were pale since the early neonatal period. The clinical feature noted to be sensitive for extra hepatic biliary atresia was the presence of acholic or varying acholic stools on admission. There was no single clinical feature with sufficient sensitivity and specificity to differentiate extra hepatic biliary atresia from other causes of neonatal cholestasis. In a study done in Malaysia in 146 infants with cholestasis, the three most common causes were INHS (n=63, 43%), extra hepatic biliary atresia (n=35, 24%) and congenital cytomegalovirus hepatitis (n=13, 9%)7. Our study also showed the same pattern except neonatal hepatitis was more common than INHS. Reason for increase frequency of neonatal hepatitis cases in our study was full evaluation of idiopathic neonatal hepatitis with complete TORCH screening.

In twenty cases of neonatal hepatitis syndrome was a complete workout for CMV infection done and seventeen of them became positive for CMV infection. One of these infants who were positive for CMV infection coexisted with biliary atresia. It is important to have a well-organized and structured approach to detect TORCH related cholestasis, in particular CMV
hepatitis because according to this study, the cases of CMV related cholestasis were underdiagnosed. Moreover, investigating and diagnosing of metabolic disorders like PFIC is also a difficult task because of financial constraint and non-availability of facilities.

Most patients in whom no aetiology was found were considered to have transient neonatal cholestasis by some authors. Transient neonatal cholestasis was characterized by: early-onset cholestasis, absence of a known cause of neonatal cholestasis, normalization of clinical and biochemical parameters during follow up, and no history of some neonatal injurious events such as asphyxia, sepsis, total parenteral nutrition[4]. As this study also had shown transient neonatal cholestasis as one of the major reasons for cholestasis.

Delay in referral of cases of neonatal hepatitis syndrome to appropriate centres is still a major problem in many parts of the world[5,6]. It was shown in a study done in India that there was a considerable delay in the referral of patients to appropriate centres for management. In a study done in India by Yachaa et.al showed a delay of 120.8 +/- 60.5 days in extra hepatic biliary atresia and 65.9 +/- 39.2 days in neonatal hepatitis syndrome were documented[5]. In our study there was a significant delay in the presentation of cases of cholestasis to hospital with the average age being 84.09 days. Infants, who were eventually diagnosed as biliary atresia presented at the mean age of 83.04 days and 85.10 days in neonatal hepatitis.

The majority of these infants were evaluated by the primary health care workers. Therefore, it is presumed that infants cholestasis presenting late, could have been minimized if a screening test like stool colour code system was available to parents and/or primary health care workers. Furthermore, the primary health care workers must be alerted when they deal with cases of infants with persistent jaundice for more than two weeks and/or with pale stool at any stage to refer them early to an appropriate centre. However, persistently clay coloured stools had a modest accuracy to differentiate extra hepatic biliary atresia from the neonatal hepatitis syndrome[7]. Studies have shown that introducing stool colour card screening system improved the outcome of extra hepatic biliary atresia by early identification and early institution of specific management[8,9]. This screening system might be especially effective in areas with a high proportion of late referrals[8].

The most common presentations of cholestasis were jaundice, hepatomegaly, pale stool, dark urine and splenomegaly. The more frequent aetiological factors for cholestasis were neonatal hepatitis syndrome and biliary atresia. Other frequent causes were idiopathic neonatal hepatitis and cholestasis with multiple problems where single aetiology could not be identified as to the cause of cholestasis. Furthermore, the study had shown a significant delay in the presentation of cases of cholestasis.

The study highlights the common etiological factors for NCS in Central India. Although complete work up was done in most patients, data on long-term outcome and follow-up is not available.

CONCLUSION:

Jaundice, hepatomegaly and pale stoolswere the common clinical features on presentation. Biliary atresia and Neonatal hepatitis were the common causes of cholestasis. TORCH infection was distinctly common in our setting. Early identification of the cause was essential for a favourable outcome. This requires specific biochemical tests, imaging studies and interpretation of histopathology by experienced personnel.

Limitation of study:

The limitations of this study is lack of patients follow up after kasai procedure. Due to the sensitive nature of the disease and the need for education of general physicians and paediatricians about the causes of cholestasis and its diagnosis, there is a need for further studies. It is suggested that more attention should be paid to genetic and metabolic disorders and also the facilities should be provided for diagnosis of these diseases in referral centres such as our centre.

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