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SPECTRUM OF NEONATAL CONJUGATED HYPERBILIRUBINEMIA IN A TERTIARY CARE HOSPITAL

Neonatology

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ABSTRACT

Background: Jaundice though common in Neonatal period is mainly unconjugated. Conjugated hyperbilirubinemia is always pathological, so it is important to understand the etiology and spectrum of conjugated hyperbilirubinemia so that it can be detected and treated early **Aim:** To study the spectrum of conjugated jaundice in babies admitted in Neonatal ICU **Methods:** It was a retrospective study conducted in the department of Neonatology of a tertiary care hospital during one year period.Babies with conjugated hyperbilinemia admitted in NICU were enrolled in the study and spectrum of the disease was studied in them. The statistical analysis was done using SPSS 20.0 **Result:** total 47 babies were enrolled, mean age of jaundice onset was 11.1 ±5.6 days, mean birth weight of neonates was 2.08± 0.88 kg, 42.6% babies were term delivery (37-42weeks), 17% late preterm (34-37 weeks) and 40.4% patients preterm delivery (< 34 weeks). Seventy-two percent were unwell at the time of presentation. Primary etiology was sepsis (51.1%), followed by multifactorial liver disease (31.9%), Ischemic (25.6%), Inspissated bile duct (8.5%), 8.5 percent cases were Idiopathic , 2.1 percent had biliary obstruction (2.1%) and TPN associated (2.1%). The most common organism isolated was Klebsiella (50%), followed by E.coli (12.5%). There is statistically significant relationship between Jaundice onset and condition at presentation ($p < 0.05$). Most common factors responsible for conjugated jaundice in current study were Mechanical ventilation 51.1%), Inotropes injection (346), recent surgery (176), PPHN (14.9%), Parenteral Nutrition (12.8%), HFOV (12.8%) and congenital heart disease (2.1%). **Conclusion:** It is one of the few studies to study the etiology and spectrum of conjugated in a tertiary care hospital.

KEYWORDS

Neonatal-jaundice, Hyperbilirubinemia, conjugated- hyperbilrubinemia

INTRODUCTION

Hyperbilirubinemia is the most common transitional finding in newborn period, occurring in 60% to 70% of term and 80% of preterm infants. Hyperbilirubinemia presents as either unconjugated hyper bilirubinemia or conjugated hyperbilirubinemia[1]. Hyper bilirubinemia in newborns is generally unconjugated. Conjugated hyper bilirubinemia (CHB) is mostly caused by intrinsic liver dysfunction. However, certain diseases cause both unconjugated and conjugated hyperbilirubinemia because they affect several different aspects of hepatocyte function[2].

Conjugated hyperbilirubinemia (CHB) is defined as a measure of direct reacting bilirubin of>1.0 mg/dL, if the total serum bilirubin (TSB) is >5.0 mg/dL, or more than 20% TSB.. The prevalence of this disorder is estimated at 1 out of every 2500 live births. Extrahepatic biliary atresia (EHBA) and idiopathic neonatal hepatitis (INH) account for two thirds of these cases[4],

The etiologies of infantile CHB are numerous. While specific symptoms might narrow diagnostic possibilities, a complete history and physical examination, diagnostic imaging and laboratory investigations directed at the more common etiologies is required to make a prompt and definitive diagnosis[5]. Early workup and diagnosis is necessary for appropriate management and prevention of future complications. Generally serum conjugated bilirubin was investigated when neonatal jaundice was prolonged beyond 14-21 days prior to that only total bilirubin was investigated[4].

The detection of CHB presenting before 14 days of life was usually triggered by specific clinical situations, hence the real incidence and etiology of CHB in neonates below 14 days were unknown[6-7]. It is a biochemical marker of cholestasis and hepatocellular dysfunction[8]. This condition is rare in the industrialized world, but it is still common in many developing countries[9]. With the aim of identifying spectrum of conjugated jaundice in neonates admitted in NICU and identifying factors and etiology responsible for it, current study had been conducted at Multispecialty hospital in National Capital.

AIM & OBJECTIVES

AIM: To study the spectrum of conjugated jaundice in neonates in the NICU

OBJECTTVES:

1. To analyze various etiologies of conjugated jaundice in neonates.
2. To study the factors responsible for early and late onset conjugated jaundice in neonates.

MATERIALAND METHODOLOGY

Study Setting: The study was conducted in the department of Neonatology of a tertiary care Hospital

Study Design: This was retrospective observational, non-randomized hospital based study.

Location Of Study: Department of Neonatology at Indraprastha Apollo Hospitals, New Delhi.

Study Population: All neonates diagnosed with Conjugated hyperbilirubinemia admitting in the NICU.

Sample Size: 47 patients

Duration Of Study: January 2020 to december 2020

Inclusion Criteria: All neonates diagnosed with Conjugated hyperbilirubinemia require admission to Neonatal ICU

Exclusion Criteria: Patients with Undiagnosed early demise within first day of life

METHODOLOGY:

Medical charts of newborns admitted to the NICU in a period between January 2020 to dec 2020 were retrospectively reviewed using the Hospital's data registry system. Conjugated hyperbilirubinemia was defined as direct bilirubin value greater than 1.0 mg/dl if total biliubinwas less than 5 mg/dl or direct bilirubin more than 20% of the total bilirubin if the total bilirubin was greater than 5 mg/dl. Clinical data, results of laboratory testing, radiological studies (if done), and outcome (death, resolving time or specific treatment) of the patients with Conjugated hyperbilirubinemia was recorded from the patients' medical files.

Along with patients' demographic details, patients' chief complaints, birth history, gestational age, gestational history, ante-natal ultrasonography evaluation suggesting any disease, intra-partum events such as birth asphyxia, hemorrhages etc., eventful postnatal course like assisted ventilation, cardiovascular incompetence and

support, exchange transfusion, infection status, and parenteral nutrition administration was recorded to indicate towards the possible etiologies.

Statistical Analysis:
All the data in current study was entered into Microsoft excel spread-sheets and analyzed with the help of software IBM SPSS version 20.0. Qualitative data such as Age group of the patients, Gender, clinical findings, birth weight classification, intra-natal and post-natal history, gestational age, etiology. Culture findings and type of treatment were expressed by using descriptive statistics such as frequency and percentages. Chi square test applied to check the statistical association in cross tabulation that made between two qualitative data. P value less than 0.05 considered as statistically significant.

Quantitative data such as age of patients, birth weight, liver function test were also expressed by mean and standard deviation. Independent sample test was also applied for checking the statistical association between two groups. P value less than 0.05 considered as statistically significant.

Observations
In the study , , with minimum 3 day and maximum 30 days of age. More than one-thirds of patients (38.4%) had jaundice between 8- 14 days age (n=18), followed by 1 - 7 days age (31.9%, n=15), 15-21 days age (27.7%, n=13), 1-3 days age (6.4%, n=3) and 22-30 days (2.1%, n=1). Out of total, 42.6% babies had term delivery (37-42weeks), while 17% patients had Late preterm delivery (gestational age 34-37 weeks) and 40.4% patients had preterm delivery (gestational age 34 weeks).

In the current study, more than two-thirds of the neonates (70.2%) were unwell at the time of presentation while remaining 29.8% neonates were clinically stable.

In the current study, mean birth weight of neonates was 2.08± 0.88 kg with minimum 0.66 kg and maximum 3.5 kg birth weight. Out of total, 44.7% neonates had normal birth weight (2.5-4.0 kg), while 19.1% neonates had low birth weight (LBW = 1.5-2.49 kg), 25.5% neonates had Very low birth weight (VLBW = 1.0 149 kg) and 10.6% neonates had extremely low birth weight (ELBW = <1.0 kg).

Among all the neonates, most common primary etiology was sepsis (51.1%), followed by multifactorial liver disease (31.9%), Ischemic (25.6%), Inspissated bile duct (8.5%), 8.5 percent cases were Idiopathic (8.5%), 2.1 percent had biliary obstruction (2.1%) and TPN associated (2.1%). Among 4 patients with inspissated bile ducts, 3 patients had required exchange transfusion.

Among 12 Ischemic patients, 5 patients had perinatal asphyxia, 3 patients had CHD, 2 patients had sepsis and 1 had perinatal asphyxia and sepsis.

Twenty four neonates had culture proven sepsis. The most common organism isolated was Klebsiella (50%), followed by E.coli (12.5%), , Pseudomonas (4.2%), Acinetobacter (4.2%), Candida (4.2%), Burkholderia (4.2%), Enterobacter Cloacae (4.2%).

In the current study, Mean values of Total, direct and Indirect bilirubin were 8.62 ±5.8, 4.22 ±3.61 & 4.4 ± 3.27 mg/dl respectively with minimum 1.4, 1.0 & 0.4 mg/dl respectively and maximum 33, 17& 16 mg/dl respectively. However, mean values of SGPT and SGOT were 59.6 ±62.5 & 101.3 ± 151.7 IU/L respectively with minimum 6 & 13 IU/L respectively and maximum 281 & 762 IU/L respectively.

In current study, more than two-thirds of the patients (70.2%) had early onset Jaundice (≤14 days), while remaining 29.8% had late onset Jaundice (>14 days).

Table 1: Comparison of baseline charecteristics between early and late onset Jaundice

Various parameters		Onset of Jaundice		P value
		Early Onset (n=33)	Late Onset (n=14)	
Sex	Male	27(81.8%)	10(71.4%)	0.426
	Female	6(18.2%)	4(28.6%)	
Gestational Age	Preterm	12(36.4%)	7(50.0%)	0.450
	Late Preterm	5(15.2%)	3(21.4%)	
	Term	16(48.5%)	4(28.6%)	
Birth Weight	Normal weight	16(48.5%)	5(35.7%)	0.080
	LBW	7(21.2%)	2(14.3%)	
	VLBW	9(27.3%)	3(21.4%)	
	ELBW	1(3.0%)	4(28.6%)	
Condition at presentation	Well	7(21.2%)	7(50.0%)	0.048
	Unwell	26(78.8%)	7(50.0%)	
Type of treatment	Medical	25(75.8%)	10(71.4%)	0.756
	Surgical	8(24.2%)	4(28.6%)	

After comparing onset of Jaundice with various other parameters had shown statistically significant relationship between Jaundice onset and condition at presentation ($p < 0.05$). However, there was statistically non-significant relationship of Jaundice onset with sex, birth weight, gestational age, type of treatment ($p > 0.05$).

Among patients with Multifactorial Liver disease (n=15), 73.3% patients had early onset Jaundice and remaining 26.7% had late onset jaundice. Among patients with Ischemic (n=12), 66.7% patients had early onset Jaundice and remaining 33.3% had late onset jaundice. Among patients with Inspissated bile duct (n=4), 75% patients had early onset Jaundice and remaining 25% had late onset jaundice. While all patients with Idiopathic cause had early onset jaundice and all patients with biliary obstruction and TPN associated had late onset jaundice.

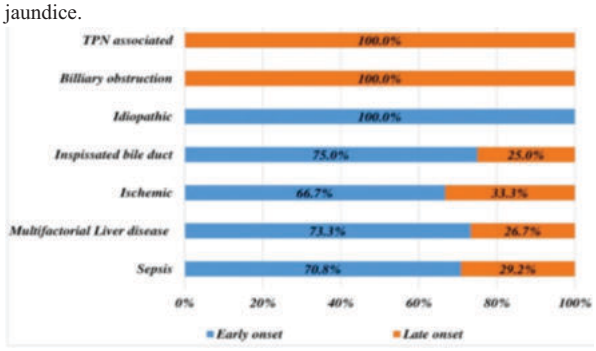

Figure 1: Distribution of patients based on onset of Jaundice and Primary Etiology

There was non-significantly higher level of Total, Direct & Indirect bilirubin and SGPT among patients with Early onset Jaundice compared to Late onset Jaundice ($p > 0.05$). However, there was non-significantly lower levels of SGOT among patients with Early onset Jaundice compared to Late onset Jaundice ($p > 0.05$).

Most common factors responsible for conjugated jaundice in current study were Mechanical ventilation 51.1%), Inotropes injection (346), recent surgery (176), PPHN (14.9%), Parenteral Nutrition (12.8%), HFOV (12.8%) and congenital heart disease (2.1%).

DISCUSSION

Conjugated hyperbilirubinemia (CHB) in a neonate may be indicative of serious hepatobiliary pathology, such as biliary atresia (BA) or inborn errors of metabolism (IEM). Based on current guidelines, conjugated bilirubin (CB) is screened when neonatal jaundice persists beyond 14-21 days. Although less routinely encountered, neonatal Conjugated hyperbilirubinemia presenting within 14 days of life can pose considerable diagnostic and management challenges.There are many causes of conjugated hyperbilirubinemia (CH) in newborn infants admitting to NICU. The immaturity of hepatobiliary system makes a newborn relatively more susceptible to a wide variety of disorders[12]

Current cross sectional study was conducted for studying the spectrum of conjugated jaundice in 47 neonates admitted in NICU. Various studies have been conducted around the world to study etiologies of conjugated jaundice among neonates. A retrospective study was also conducted by Ipek et al[10] for determining underlying causes and short-term prognosis of patients with conjugated hyperbilirubinemia in 104 neonates. A retrospective review was conducted by Tiker el al[3] for determining causes and related outcomes of early onset conjugated hyperbilirubinemia in 42 newborn infants. A cross-sectional study conducted by Carneiro et al[14] among 83 neonates with neonatal cholestasis in a level II NICU for identifying predictors of mortality. Similarly, a retrospective review done by Chiou et al[11] described

etiology and characteristics of early-onset conjugated hyper bilirubinemia presenting within 14 days of life in 117 term neonates. Also a retrospective review done by Aanpreung et al [15] studied etiologies and outcome of neonatal cholestasis in 252 Thai infants. A cohort study done by Gottesman et al[5] for determining prevalence rates of specific etiologies of conjugated hyper bilirubinemia in infancy.

Age and sex of the neonates

In the current study, mean age of babies was 11.1±5.6 days, with majority were 8- 14 days (38.49%) and 1 -7 days age (31.9%) and were males (78.7%) with male - female ratio of 3.1:1. Among males, majority (40.5%) were 1 -7 days old, while among females majority were 8-14 days old (60%), this relationship of age and sex of patients was statistically significant (p<0.05). Mean age of presentation with jaundice in Tiker el al[3] was 10 days. Ipek et al[10] had found mean postnatal age at diagnosis of CH was 14.3±16.9 days, while 51.1% infants develop CH in first week of life. Male predominance was also found in a study conducted by Ipek et al [10] (56.5%), Aanpreung et al[15] (53.6%) and Carneiro et al[14] (60%).

Gestational age and Birth weight of neonates

In the present study, majority of patients (42.6%) had full term delivery, while 17% patients had late preterm delivery and 40.4% had preterm delivery. Though, mean birth weight of patients was 2.08 ±0.88 kg, while majority of patients (44.7%) had normal birth weight, followed by VLBW (25.59%), LBW (19.1%) and ELBW (10.69%). In study done by Ipek et al[10] had found mean gestational age of premature infants was 31.3±3.2 weeks and mean birth weight was 1.63±0.6 kg, while 47.2% preterm infants had VLBW, and 15.2% infants were small for gestational age (SGA). In Tiker el al[3] study, mean gestational age was 37 weeks. In Carneiro et al[14] study, 78.3% newborns were preterm, mean gestational age was 32±5 weeks and median birth weight was 1.364 kg.

Clinical condition on presentation

In the current study, more than two-thirds of the patients (70.2%) had unwell condition at presentation, while 29.8% patients were in well condition at presentation. A study by Chiou et al[11] had found significantly relationship for clinically ill status at presentation among early onset Jaundice patients (80%) and late onset Jaundice patients (42.3%). As per guidelines, healthy infants below 14 days with jaundice are rarely tested for conjugated bilirubin, potentially missing conjugated hyperbilrubinaemia in healthy patients. Our study had more unwell neonates which had conjugated jaundice, this was attributed to the fact that our hospital is tertiary care referral center with a Level 3 NICU.

Primary etiology of Conjugated hyperbilirubinemia

In the present study, most common primary etiology was sepsis (51.1%), followed by multifactorial liver disease (31.9%), Ischemic (25.6%), Inspissated bile duct (8.59%), Idipathic (8.5%), biliary obstruction (2.1%) and TPN associated (2.1%). In Ipek et al[10] study, commonest causes of CH were Ischemia (30.4%), inspissated bile (22.8%), infection (9.8%), inherited metabolic disorder (12%), and CHD (5.4%), biliary duct obstruction (5.4%), bile duct paucity syndromes (3.3%). In Aanpreung et al[15] study, commonest etiologies for neonatal cholestasis were INH (23%), EHBA (22.29%6), TPN-related cholestasis (18.3%), infection (9.9%),miscellaneous causes (9.1%), endocrine cause (6%), choledochal cyst (5.6%), Down syndrome (4.4%) and hemolytic anemia (1.6%).

A study done by Fischler et al[16] had found commonest diagnosis for neonatal cholestasis were extrahepatic biliary atresia (35.3%), a-antitrypsin deficiency (12.9%) and progressive familial intrahepatic cholestasis (12.9%). Commonest etiological causes in Gotesman et al[5] study were Idiopathic neonatal hepatitis (26%), extrahepatic biliary atresia (25.9%), infection (11.5%). TPN- associated cholestasis (6.4%), metabolic disease (4.4%), alpha-1 anti-trypsin deficiency (4.16), and perinatal hypoxia/ischemia (3.7%). A study by Carneiro et al[14] had found multifactorial etiology for cholestasis among them commonest etiology were sepsis (80.7%),digestive diseases (49.4%), Non-cardiac surgery (45.8%), bronchopulmonary dysplasia (21.7%), necrotizing enterocolitis (15.7%) and others. This can be attributed to the fact that our study was conducted in a developing country where sepsis is more prevalent than the developed countries.

Culture findings

In the current study, among the neonates having conjugated jaundice culture proven sepsis was present in 51.1 percent neonates. Blood culture findings found commonest organisms were Klebsiella, E.coli, Candida, Pseudomonas, Acinetobacter, Burkholderia, Enterobacter Cloacae. In similar study conducted by Ipek et al[10], culture findings among infectious causes had found commonest organisms were Candida, CMV hepatitis, congenital syphilis. A study by Tiker el al[3] had found that culture-proven sepsis was identified in 35.7% babies, among them Gram negative bacteria were isolated in 23.8% cases and E. coli was most common of these agents (16.7%). Among Gottesman et al[5] study, among patients with infectious causes, commonest infection were CMV (33.5%), congenital syphilis (10.8%), and E. coli (9.8%). In Aanpreung et al[15] study, commonest infectious causes were CMV, HIV, Rubella, Syphilis & Toxoplasmosis.

Liver function test of CH neonates

In current study, mean levels of Total, Direct and Indirect bilirubin were 8.62±5.8, 4.22±3.61 & 4.4±3.27 mg/dl respectively, while mean values of SGPT and SGOT were 59.6± 62.5 & 101.3 ±151.7 IU/L respectively. In Ipek et al study[10], Liver enzymes were elevated more than 10 times of upper limit among patients with ischemic causes.

A retrospective study by Davis et al had found that Conjugated bilirubin levels between 0.5 and 1.9 mg/dL could be associated with infection, but most often remain unexplained. Liver and biliary disease become increasingly likely as CB levels increase; for Conjugated bilirubin ≥5 mg/dL, 47% of newborns have biliary disease and 43% have liver disease. Though in Carneiro et al[14] study, median levels of Total and Direct bilirubin were 10.3 & 7.0 mg/dl respectively.

Onset of Jaundice and relation with various parameters

In the current study, 70.2% patients had early onset Jaundice (≤14 days), while 29.8% had late onset Jaundice (>14 days). Furthermore, there was statistically significant relationship between Jaundice onset and condition at presentation (p<0.05), but statistically non-significant relationship of Jaundice onset with sex, birthweight, gestational age, type of treatment (p>0.05). Similar findings had been found by study done by Chiou et al[11], as they found early onset jaundice in 55.6% neonates and late onset jaundice in 44.4% patients. They found that there was non-significant relationship of sex, gestational age, birth weight, APGAR score at 1 minute and 5 minutes and Cesarean section delivery with onset of conjugated hyperbilirubinemia.

Onset of Jaundice and Primary etiology

In the present study, among patients with sepsis, 70.8% patients had early onset and 29.2% had late onset jaundice. Among patients with Multifactorial Liver disease, 73.3% patients had early onset and 26.7% had late onset jaundice. Among patients with Ischemic, 66.7% patients had early onset and 33.3% had late onset jaundice. Among patients with Inspissated bile duct, 75% patients had early onset Jaundice. While all patients with Idiopathic cause had early onset jaundice and all patients with biliary obstruction and TPN associated had late onset jaundice.

A study by Chiou et al[11] had found significant relationship of multifactorial liver injury, non-hepatic cause and idiopathic causes with onset of jaundice (p<0.05), while there was statistically non-significant relationship of non-surgical causes, sepsis, inborn error of metabolism, surgical causes, biliary atresia and choledochal cyst with onset of jaundice (p>0.05). Tiker el al[3] had found commonest cause of conjugated hyperbilirubinemia were sepsis (35.7%), Perinatal hypoxia-ischemia (16.7%), blood group incompatibility (11.9%), down syndrome (7.1%), cholestasis associated with parenteral nutrition (7.1%), neonatal hepatitis (4.8%), metabolic liver disease (2.4%), biliary atresia (2.4%) and portal venous thrombosis (2.4%). Since most of our patients had a non hepatic cause, this explains why there were mostly early onset jaundice in oursetup.

Liver function test with onset of Jaundice

In the current study, non-significantly higher level of Total, Direct & Indirect biliubin and SGPT and non-significantly lower levels of SGOT among patients with Early onset Jaundice compared to Late onset Jaundice (p>0.05). A study by Chiou et al[11] had significantly higher level of Total bilirubin, and significantly lower level of ALP and GGT among patients with Early onset Jaundice compared to Late onset Jaundice (p<0.05). Moreover, they found non-significantly higher levels of conjugated bilirubin and AST and non-significantly lower levels of conjugated fraction percent and ALT among patients with Early onset Jaundice compared to Late onset Jaundice (p>0.05).

Factors contributing to conjugated Jaundice other than primary factors

In the present study, commonest secondary factors responsible for conjugated jaundice were Mechanical ventilation (51.1%), Inotropes injection (34%), recent surgery (17%), PPHN (14.9%), Parenteral Nutrition (12.89%), HFOV (12.8%), Sepsis (6.4%) and Congenital heart disease (2.1%).

A study by Chiou et al[11] had found commonest factors responsible for multifactorial liver injury were antibiotics use (98.2%), parenteral nutrition (89.5%), sedative or opioid use (75.49%),mechanical ventilation (66.7%), inotropic support (56.1%), recent surgery (56.1%), PPHN (40.4%), intestinal obstruction (35.1%), congenital heart diseases (28.1%), HFOV (24.6%),pneumothorax (15.8%), CDH (15.8%), MAS (14%), Renal impairment (14%) and others. In Carneiro et al[14] study, total parentral nutrition was provided to 85.59% babies and recent surgery was also performed in 54.2% babies.

In Aanpreung et al[15] study, miscellaneous causes responsible for neonatal cholestasis other than primary factors were Hypoxia (2.4%), Unknown causes with normal GGT (2%),Alagille syndrome (0.8%) and others. A past study had found that among infants, most consistently reported risk factor for parenteral nutrition-associated CH was duration of parenteral nutrition. The only known effective modality was transition to full enteral feeding and discontinuation of parenteral nutrition,

CONCLUSION

It was a cross sectional study done on neonatal conjugated jaundice and found that majority of the neonates were affected in first two weeks of life (Early onset jaundice), males were more commonly affected and relation of age and sex was statistically significant. At presentation to the hospital, most babies had unwell condition. Commonest factors responsible for conjugated jaundice were sepsis, multifactorial liver disease and Ischemic with most neonates being preterm. Onset of Jaundice had statistically significant relationship with condition at presentation but had non-significant relationship with sex, birthweight, gestational age, type of treatment and Liver function test. Commonest Secondary factors responsible for conjugated jaundice and multifactorial liver disease were Mechanical ventilation, Inotropes injection, recent surgery, PPHN, Parenteral Nutrition, HFOV, Sepsis and congenital heart disease.

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