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Original Research Article

An Observational Retrospective Evaluation of Neonatal and Maternal Risk Factors for Indirect Hyperbilirubinemia

Bheemsen Kumar[1], Sanjay Kumar Nirala[2], Sanju Kumari[3], Gopal Shanker Sahni[4]

[1]Senior Resident, Department of Pediatrics, SKMCH, Muzaffarpur, Bihar, India.
[2]Senior Resident, Department of Pediatrics, SKMCH Muzaffarpur, Bihar, India
[3]Junior Resident, Department of Obstetrics and Gynecology, Nalanda Medical College and Hospital, Patna, Bihar India
[4]Associate Professor and HOD, Department of Pediatrics, SKMCH, Muzaffarpur, Bihar, India

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Corresponding author: Dr. Sanjay Kumar Nirala
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Abstract

Aim: This study was aimed at determining neonatal and maternal risk factors of indirect hyperbilirubinemia, at comparing neonates with risk factors and those without, and at assessing the type of management according to hyperbilirubinemia severity.

Methods: This study was an observational retrospective study conducted Pediatrics Department at SKMCH, Muzaffarpur, Bihar, India for one year. Data was collected and reviewed through electronic and printed medical records of all neonates. Initially, 575 medical records were reviewed. Duplicate registries of those who were readmitted for indirect hyperbilirubinemia management (n = 32) were removed, and they were included in the total data only once of the first presentation. Patients with insufficient data (n = 43) were also removed as a first step. Total 500 neonates were included in the study.

Results: In the present study, there were 52% were male neonates and 48% females neonates. 80% neonates were full term. 60% women belonged to age group 25-35 years. 65% women underwent normal vaginal delivery. 40% new borns and 60% mothers had O blood group. 95% new borns and 90% mothers had positive Rh factor. Of 500 neonates, 400 (80%) had risk factors for neonatal indirect hyperbilirubinemia. ABO incompatibility is the commonest factor and was found in 200 (40%) patients, followed by G6PD deficiency which was found in 160 (32%). Maternal age (>25 years) was the commonest risk factor and found in 420 (84%) mothers, followed by cesarean section delivery, which was found in 160 (32%) mothers. Three (1.7%) neonates had positive blood cultures. Seven neonates had positive urine cultures (8%). The rest showed mixed growth between the previous organisms (9.3%). Skull ultrasound was done for 35 (8.7%) infants. Abdominal ultrasound showed hepatosplenomegaly and biliary sludge, each in two patients.

Conclusion: ABO incompatibility, G6PD deficiency, and older maternal age (>25 years) were the commonest neonatal and maternal risk factors for developing neonatal indirect hyperbilirubinemia. Male newborns, reticulocytosis, and IVIG use were associated with these factors.

Keywords: Hyperbilirubinemia, Neonatal, Maternal, Risk Factor.

Introduction

Neonatal jaundice is a common event that occurs especially in the first week of birth [1-3] and is one of the most common causes of hospitalisation of the term and preterm neonates in neonatal wards. [1] Based on the present evidence, 80% of premature infants have clinical symptoms, including yellowish skin and sclera, caused by serum bilirubin levels. [4,5] Hyperbilirubinemia is a common disease that occurs especially in the first week of birth [1-3] and is one of the most common causes of hospitalisation of the term and preterm infants in neonatal hospitals. [1] It usually occurs on the second day of birth and is not usually harmful, and a self-limiting condition, where disease usually improves without treatment after reaching the normal amount of bilirubin [6,7], but very high levels of bilirubin may lead to kernicterus as permanent brain damage. Nevertheless, diagnosis of newborn jaundice and its management will play an important role in the health of newborns. [8] If jaundice lasts more than 14 days, it is called to be prolonged neonatal jaundice. [6]

An imbalance between bilirubin production and conjugation is the main mechanism of jaundice, which leads to an increase in bilirubin levels. [9]

This imbalance often occurs due to the immature liver and the rapid breakdown of red blood cells, which may be involved with several factors. [10-12] The risk factors of neonatal hyperbilirubinemia are diverse, complex and interconnected. For example, the age and gestational age of the pregnant woman will affect or change the feeding mode, and perinatal diseases may affect the delivery method, causing a series of chain reactions. Chen et al [13] believed that exclusive breastfeeding was a risk factor. Scrafford et al14 believed that exclusive breastfeeding may be a protective factor for specific neonatal hyperbilirubinemia. Chen et al [15] concluded that high breastfeeding frequency can reduce the incidence of hyperbilirubinemia. Huang et al [16] considered that preterm birth, exclusive breastfeeding, blood group incompatibility, and glucose-6-phosphate dehydrogenase (G6PD) deficiency are risk factors for the disease. Kaplan et al [17] considered that only G6PD, blood group inappropriate disease risk factors.

The socioeconomic conditions and cultural background of different regions may have some influence on the results. Therefore, it is of great clinical significance to determine the risk factors of neonatal jaundice to effectively reduce the risk of neonatal hyperbilirubinemia and the incidence of related complications. Most of the studies are retrospective analysis, the sample size is small, and the evidence level is low, which cannot support the conclusion.

This study was aimed at determining neonatal and maternal risk factors of indirect hyperbilirubinemia, at comparing neonates with risk factors and those without, and at assessing the type of management according to hyperbilirubinemia severity.

Materials and Methods

This study was an observational retrospective study conducted Pediatrics Department at SKMCH, Muzaffarpur, Bihar, India for one year. Data was collected and reviewed through electronic and printed medical records of all neonates. Initially, 575 medical records were reviewed. Duplicate registries of those who were readmitted for indirect hyperbilirubinemia management (n = 32) were removed, and they were included in the total data only once of the first presentation. Patients with insufficient data (n = 43) were also removed as a first step. Total 500 neonates were included in the study.

Inclusion Criteria

All neonates admitted for evaluation, investigation, and management of neonatal indirect hyperbilirubinemia were included.

Exclusion Criteria

Patients were excluded from the study if they presented to the hospital with neonatal jaundice but were not admitted and if they were diagnosed with direct hyperbilirubinemia.

Data Collection

Maternal risk factors of neonatal indirect hyperbilirubinemia including maternal age if >25 years, maternal race if East Asian, gestational diabetes (GDM) or diabetes mellitus (DM), urinary tract infection (UTI) in mothers, hypothyroidism, hyperthyroidism, and the mode of delivery were collected. Neonatal demographic data including sex, nationality, age at presentation, gestational age, birth weight, feeding type, management, and length of hospital stay were also gathered.

Laboratory evaluations include complete blood count (CBC) with differentials, reticulocyte count, maternal and newborn blood group and Rh factor, liver function test (LFT), total serum bilirubin (TSB) and indirect serum bilirubin (ISB) levels at admission, direct Coombs test (DCT), serum free thyroxine (T4) and thyroid-stimulating hormone (TSH) levels, blood and urine cultures, TORCH screen, erythrocyte G6PD status (deficiency if <650 U/L in males or <400 U/L in females), and hemoglobin electrophoresis. The need for phototherapy and double-volume whole blood ET, including the duration of phototherapy, was also included. Kernicterus was suspected in patients who had early neurological symptoms and signs. Radiological imaging such as skull ultrasound, computed tomography scans, and magnetic resonance imaging of the brain was reviewed for those patients.

Ethical Consideration

This study was conducted in agreement with the Helsinki Declaration and was approved by the Research and Research Ethics Committee. Informed consent was obtained from each infant's parent or legal guardian upon admission.

Statistical Analysis

Data were initially entered in Excel sheet and then transferred to IBM SPSS Statistics program version 21.0 (IBM Co., Armonk, NY, USA) for analysis. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as mean and standard deviation or median and interquartile range (IQR) according to distribution normality. The Kruskal-Wallis test was used to compare different types of phototherapies while the Mann–Whitney U test was used to compare neonates who received ET and/or IVIG with those who did not in terms of the mean indirect bilirubin level. To study the possible risk factors for hyperbilirubinemia, patients were

divided into two groups, neonates with risk factors (one or more) and those without. Both groups were compared using Fisher's exact test or Pearson's chi-square test for categorical variables (sex, nationality, mode of delivery, phototherapy, and IVIG use). Continuous variables (white blood cell count, hemoglobin, hematocrit, platelets, and reticulocyte percentage) were compared using the Student T test or Mann–Whitney U test. Moreover, to differentiate hemolytic disease of the newborn (HDN), such as ABO compared in terms of the mean serum indirect bilirubin level using the Mann–Whitney U test. P value < 0.05 was considered statistically significant. Confidence interval was set at 95%.

Results

Table 1: Demographic data

Gender	**N%**
Male	260 (52)
Female	240 (48)
Age at presentation (day), median (IQR∗)	2 (1-3)
Within 24 hours	200 (40)
1-5 days	275 (55)
>5 days	25 (5)
Gestational age (week), median (IQR)	38 (37-39)
Term	400 (80)
Preterm	100 (20)
Birth weight (kg), median (IQR)	3 (2.6-3.3)
Maternal age (year)	
<25	75 (15)
25-35	300 (60)
>35	125 (25)
Mode of delivery	
Normal Vaginal	325 (65)
LSCS	175 (35)
Newborn blood group	
O	200 (40)
B	150 (30)
A	125 (25)
AB	25 (5)
Maternal blood group	
O	300 (60)
B	100 (20)
A	80 (18)
AB	10 (2)
Newborn Rh factor	
Positive	475 (95)
Negative	25 (5)
Maternal Rh factor	
Positive	450 (90)
Negative	50 (10)
Hospital stays (day), median (IQR)	3 (2-5)

In the present study, there were 52% were male neonates and 48% females neonates. 80% neonates were full term. 60% women belonged to age group 25-35 years. 65% women underwent normal vaginal delivery. 40% new borns and 60% mothers had O blood group. 95% new borns and 90% mothers had positive Rh factor.

Table 2: Neonatal and maternal risk factors for the development of neonatal indirect hyperbilirubinemia

Neonatal Factors	**N%**
Indirect hyperbilirubinemia.	400 (80)
ABO blood group incompatibility	200 (40)
Glucose-6-phosphate dehydrogenase deficiency	150 (30)
Prematurity	100 (20)
Polycythemia	40 (8)
Rhesus factor incompatibility	35 (7)

Cephalohematoma	10 (2)
Sepsis (n = 150)	3 (2)
Congenital hypothyroidism (n = 160)	1 (0.62)
Maternal risk factors n (%) Maternal age > 25 years	420 (84)
Cesarean delivery	160 (32)
Maternal race	105 (21)
Gestational diabetes/diabetes mellitus	75 (15)
Maternal hypothyroidism	45 (9)
Maternal UTI	10 (2)
Maternal hyperthyroidism	2 (0.4)
No maternal risk factors determined	50 (10)

Of 500 neonates, 400 (80%) had risk factors for neonatal indirect hyperbilirubinemia. ABO incompatibility is the commonest factor and was found in 200 (40%) patients, followed by G6PD deficiency which was found in 160 (32%). Maternal age (>25 years) was the commonest risk factor and found in 420 (84%) mothers, followed by cesarean section delivery, which was found in 160 (32%) mothers.

Table 3: Laboratory tests and radiological imaging of 404 neonates with indirect hyperbilirubinemia

Investigations	Results
Hemoglobin (g/dL), mean ± SD	16.6 ± 2.4
Hematocrit (%), mean ± SD	52.8 ± 7.6
Platelets count, median (IQR)	260 (202-337.8)
White blood cell count, median (IQR)	10.5 (8.4-13.5)
Reticulocytes (%), median (IQR)	3.7 (1.4-5.4)
Total serum bilirubin (µmol/L), median (IQR)	238 (188-292)
Indirect bilirubin (µmol/L), median (IQR)	220 (174-270)
Thyroid stimulating hormone (µIU/mL), median (IQR) (n = 160)	3.5 (2.4-5.8)
Free thyroxin (T4) (µg/dL), median (IQR) (n = 50)	27.3 (23.9-32.5)
Positive neonatal blood culture (n = 170)	3.0 (1.7)
Positive neonatal urine culture (n = 90)	8 (8.8)
Positive maternal urine culture (n = 250)	25 (10)
Positive maternal high vaginal swab (n = 100)	40 (40)
Positive HPLC (n = 400)	120 (30)
Skull ultrasound (n = 30)	1 (3.3)
Abdominal ultrasound (n = 20)	2 (10)

Three (1.7%) neonates had positive blood cultures. Seven neonates had positive urine cultures (8%). The rest showed mixed growth between the previous organisms (9.3%). Skull ultrasound was done for 35 (8.7%) infants. Abdominal ultrasound showed hepatosplenomegaly and biliary sludge, each in two patients.

Table 4: Type of management for 404 neonates with indirect hyperbilirubinemia

Management	N (%)	Indirect bilirubin level (µmol/L)	P value
Phototherapy type	425 (85)		<0.0001
Single	225 (45)	198.2 ± 60.2	
Double	125 (25)	259.9 ± 67.3	
Triple	75 (15)	292.4 ± 70.4	
Exchange transfusion use			0.640
Yes	25 (5)	266.4 ± 140.20	
No	475 (95)	226.4 ± 72.8	
IVIG use			0.005
Yes	50 (10)	257.3 ± 80.5	
No	450 (90)	225.5 ± 75.5	

Data about phototherapy use was found in 425 (85%) patients. The use of phototherapy significantly increased along with the rise of the mean indirect bilirubin level (P < 0.0001). Neonates who received ET had higher mean level of indirect bilirubin, but this difference was not statistically significant (P = 0.640). Yet, neonates who received IVIG had significantly higher indirect bilirubin levels compared to those who did not (P = 0.005).

Table 5: Comparison between neonates with risk factors of indirect hyperbilirubinemia versus those without

Variables	Neonates with risk factors, n % = 400 (80%)	Neonates without risk factors, n % = 100 (20%)	P value
Gender			
Male	280	35	0.009
Female	120	65	
Mode of delivery			
Normal Vaginal	260	55	0.001
LSCS	240	45	
WBC, mean ± SD	11:3 ± 4:67	12:1 ± 4:3	0.13
Hematocrit, mean ± SD	53:8 ± 8:3	54:4 ± 5:5	0.39
Hemoglobin, mean ± SD	16:8 ± 2:3	17:2 ± 2:1	0.08
Platelets, mean ± SD	275 ± 97:3	272:3 ± 104:1	0.77
Reticulocytes, mean ± SD	4:6 ± 2:6	3:7 ± 1:8	0.001
Total bilirubin, mean ± SD	247:9 ± 82:3	246:5 ± 75:5	0.888
Indirect bilirubin, mean ± SD	228:8 ± 78:9	230:5 ± 71:9	0.864
Phototherapy use N=425	375	50	0.840
Single	275	20	
Double	70	18	
Triple	30	12	
IVIG use	50	0	0.001
Exchange transfusion use	22	3	0.165

On comparing newborns with risk factors (one or more) to those without, male (P = 0.009) newborns, those with high reticulocytes (P = 0.001), and those who received IVIG were more prone to have associated risk factors of neonatal indirect hyperbilirubinemia. However, mode of delivery; other laboratory investigations such as white blood cell count, hematocrit, hemoglobin level, platelets, total bilirubin, and indirect bilirubin; phototherapy use; and ET were not associated with the presence of neonatal indirect hyperbilirubinemia risk factors.

Discussion

Neonatal jaundice is the clinical manifestation of hyperbilirubinemia. [18] It is the most common cause of admission in neonates worldwide. [19] It is defined as the yellowish discoloration of the sclera, skin, and mucus membranes due to bilirubin deposition. It occurs mainly during the first week of life affecting almost 60% and 80% of term and preterm neonates, respectively. [19] It occurs when the total serum bilirubin levels exceeded 5 mg/dL. [18,20] Bilirubin is a byproduct of red blood cell (RBC) destruction. Initially, hemoglobin is released; then, it gets broken down in the spleen, liver, and bone marrow to form unconjugated bilirubin. [21] Jaundice is one of the commonest clinical conditions in newborns. [22] It is the yellow discoloration of skin, sclera and mucous membrane which occurs due to accumulation of unconjugated, lipid soluble bilirubin pigment in the skin encountered during the neonatal period, especially in the first week of life. [23,24] The global incidence of neonatal jaundice varies with ethnicity and geography. Incidence is higher in East Asians and American Indians and lower in Africans. [25]

Of 500 neonates, 400 (80%) had risk factors for neonatal indirect hyperbilirubinemia. ABO incompatibility is the commonest factor and was found in 200 (40%) patients. Maternal age (>25 years) was the commonest risk factor and found in 420 (84%) mothers, followed by cesarean section delivery, which was found in 160 (32%) mothers. This result was supported by other studies in Saudi Arabia (31.6%), Egypt (12.9%), and Iran (16.9%) that also proved ABO incompatibility to be one of the commonest risk factors. [20,26,27] After ABO incompatibility G6PD deficiency which was found in 160 (32%). G6PD is one of the most common enzyme deficiencies globally; it affects approximately 200 million individuals. [26] Neonatal asphyxia can inhibit the activity of uridine diphosphate glucuronyl transferase (UDPGT) in the liver, consequently increasing the level of unconjugated bilirubin. Cephalohematoma or ecchymosis can lead to extravascular hemolysis, consequently increasing the level of bilirubin.

In terms of maternal risk factors, in this study, 85% of neonates were born to mothers aged older than 25 years, making it the most common maternal factor for the development of indirect hyperbilirubinemia. Similarly, Sroufe et al. considered age of more than 25 years as a risk factor. [28] Girma also concluded that most mothers of patients with neonatal indirect hyperbilirubinemia were between 25 and 29 years. [29] However, maternal age cut point varied among studies. Two cross-sectional studies from Iran

considered the age extremes, less than 18 and more than 35 years, as a risk factor. [30,31] In the current study, the newborns had cesarean delivery as the second maternal risk factor. Moreover, Abd Elmoktader et al. found that cesarean delivery was more commonly seen in neonatal indirect hyperbilirubinemia cases. [32]

Upon comparison of neonates with risk factors and those without, males were significantly higher compared to females (51.7% versus 48.3%, respectively) (P = 0:008). Most studies agreed that male sex is a contributing factor for the development of neonatal indirect hyperbilirubinemia. [28,33] Even in the United States of America, the percentage of males that developed indirect hyperbilirubinemia and kernicterus as a complication reached up to 67% of total infants, as reported by Johnson et al. [34] These findings can explain why G6PD deficiency was a common risk factor, being an X-linked recessive disease, which is more in males. On the contrary, Garosi et al. from Iran found that female sex is associated with a severe form of indirect hyperbilirubinemia. [35] Different types of therapies were used to manage indirect hyperbilirubinemia. Phototherapy is the primary treatment of indirect hyperbilirubinemia as it is a safe and effective method in lowering bilirubin levels. [20]

Conclusion

ABO incompatibility, G6PD deficiency, and older maternal age (>25 years) were the commonest neonatal and maternal risk factors for developing neonatal indirect hyperbilirubinemia. Male newborns, reticulocytosis, and IVIG use were associated with these factors. With the help of current screening methods, early detection of such risk factors is achievable. This is essential to prevent serious complications of neonatal indirect hyperbilirubinemia. Further studies are needed to evaluate the role of minor blood group incompatibility in the development and severity of neonatal indirect hyperbilirubinemia.

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