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Root Causes for Late Presentation of Severe Neonatal Hyperbilirubinemia

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Abstract:
Background: Hyperbilirubinemia (NH) in neonates is a frequent occurrence. NH is usually temporary and innocuous. Neonatals may, nevertheless, have kernicterus and encephalopathy in situations with severe NH. These negative aftereffects may be avoided with the right screening and care. Examining the social, cultural, educational, and systemic aspects of neonatal hyperbilirubinemia in newborns is the goal of this project.
Methods: 350 patients with hyperbilirubinemia who were hospitalised to the Neonatal Intensive Care Unit in the Paediatric Department at Benha University Hospital, BENch at Benha, and Al Mabarra Insurance Hospital at Tanta were the subjects of this cross-sectional research. Every newborn had regular laboratory testing, a clinical examination, and a history.
Results: At this study, Total serum bilirubin (TSB) level and baby age (in hours) had a very statistically significant positive connection (rho = 0.561, P = 0.000). Higher gestational age, higher birth weight, greater reticulocyte count, and longer age (hours) were all significant positive predictors of higher TSB level ($p<0.05$) in univariant analysis. Conversely, a higher TSB level was significantly predicted by a lower haemoglobin level. Age (hours), gestational age (weeks), and reticulocyte count were all revealed to be significant predictors of elevated TSB level in the multivariant analysis ($F=37.7$, $p=0.000$).
Conclusions: in newborns up to 14 days of age. The incidence of hyperbilirubinemia may be predicted by age, gestational age, and reticulocyte count.

Keywords: Neonatal Jaundice, severe, late presentation.

Introduction:
More than 60% of healthy term and late preterm newborns suffer from neonatal jaundice, which is often regarded as a benign, self-limiting disorder [1]. NNJ, the most frequent reason for hospitalisation or readmission during the first week of life, affects most babies [2].
On the other hand, kernicterus and irreparable brain damage may result from severe newborn hyperbilirubinemia [3]. With a frequency of 2.5% to 3.4% of hospital admissions during the newborn era, acute bilirubin encephalopathy is still a prevalent clinical finding in Nigeria [4].
The potentially fatal neurotoxic consequences of severe newborn jaundice are now uncommon due to successful early identification and postnatal treatment measures both before and after hospital discharge [5].
In the bloodstream, bilirubin is attached to albumin. Increased blood levels of free or unbound bilirubin occur once the albumin binding sites are saturated. Because of its neurotoxicity, this unbound bilirubin may penetrate the blood-brain barrier and harm the brain. Severe newborn hyperbilirubinemia may cause acute bilirubin encephalopathy, which can have long-term effects on surviving children, such as athetoid cerebral palsy, deafness, and ocular muscle paralysis. [6,7] These aftereffects are minimised when newborns with hyperbilirubinemia are identified promptly and treated appropriately.[8] Over the last 20 years, postpartum hospital stays have decreased. The majority of newborns with severe jaundice are readmitted from their homes.[9] The moms don't know enough about newborn jaundice. Mothers' understanding of hyperbilirubinemia is significantly influenced by their educational attainment and whether or not they have a history of jaundice in their kids.[10]

Patients and Methods
Between November 2022 and November 2023, 350 patients admitted to the paediatric department at Benha University Hospital, BENch in Benha, and Al Mabarra Insurance Hospital at Tanta participated in this cross-sectional research.
Inclusion criteria Infants of both sexes who had hyperbilirubinemia between birth and 14 days of age required admission to the neonatal intensive care unit (NICU) for intense phototherapy, intravenous immunoglobulin G, or exchange transfusions.
Exclusion criteria were infants whose parents declined to participate and infants with bilirubin levels that did not need NICU care.
Methods: A thorough history, general, systemic, and neurological examination were performed on each patient. laboratory tests such as direct serum bilirubin and total serum bilirubin.
Maternal blood group, infant blood group, reticulocyte count, and full blood count (CBC).
In order to investigate the causes of delayed admission of infants with newborn hyperbilirubinemia, we sent a survey questionnaire to parents. The institutional review board of Benha University gave its approval to the research and the

questionnaire. There were 47 items on the survey covering different facets of managing newborn hyperbilirubinemia.

Ethical consideration:

The work was submitted with permission code (MS 4-12-2022) to the Benha University Faculty of Medicine's Research Ethics Committee. Prior to their involvement in this research, the parents gave their informed permission.

Statistical analysis:

SPSS v26 was used to do the statistical analysis (IBM Inc., Armonk, NY, USA). The mean and standard deviation (SD) were used to display quantitative information. Frequencies and percentages (%) were used to display the qualitative factors. Additionally, the association between multiple independent variables (multivariate) was estimated using logistic regression.

Results:

Infants hospitalised with neonatal jaundice had an average age of [range 4-300 hours]. The majority of the study's neonates (23.7%) were four days old, with the next oldest group (20%) being three days old. 14.3% of newborns are 6 days of age or older. Males made up around 51.7% of the study's neonates. The maternity hospital evaluated 73.1% of the newborns. Only 23.4% and 8% of parents who got particular instructions or plans for jaundice at the maternity hospital had their total serum bilirubin levels tested there. Because over 58% of parents thought jaundice was a common baby symptom, they delayed seeking medical attention. The majority of individuals (35.4%) had jaundice due to ABO incompatibility, with Rh incompatibility accounting for 28.3% of cases. In 6.6% of instances, both Rh and ABO incompatibility were found. **Table 1**

Table (1):

Parameters	**Total Number (N= 350)**	
Age of babies (hours)	**Mean ±SD (range)**	**84.53 ± 55.76 (4-300)**
6^{th} day (**n, %)**	19 (5.4%)	
$\geq 7^{th}$ day up to 12.5 days **(n, %)**	31 (8.9%)	
Sex of babies	Male	181 (51.7%)
	Female	169 (48.3%)
Examination done at maternity hospital	Yes	256 (73.1%)
	No	94 (26.9%)
If received any specific instructions or plans concerning jaundice at maternity place	Yes	28 (8%)
	No	322 (92%)
TSB measured at maternity hospital	Yes	82 (23.4%)
	No	268 (76.6%)
Belief that jaundice is a normal finding in newborns	Yes	204 (58.3%)
	No	146 (41.7%)
Main etiological causes of neonatal jaundice		
Rh incompatibility	99 (28.3%)	
ABO incompatibility	124 (35.4%)	
Rh & ABO incompatibility	23 (6.6%)	
Unknown causes	104 (29.7%)	

The mean age of mothers (in years) was [range 19-43 years]. About 51.1 % of them came from rural areas. Majority of mothers (46.3%) were graduated from universities and 54.3% were housewives with no governmental or private sector occupation. Half of the mothers (50.3%) were multigravida. Positive consanguinity was detected in 47.1% of the study group. About two third of mothers delivered by cesarian section (65.1%). 43.1% of mothers delivered at General hospital, 43.1% at private hospital, 13.4% in a private clinic and 0.3% delivered at home. **(table 2)**

Table (2): Demographic data of mothers to infants admitted with neonatal jaundice (N=350).

Variable		Statistics (N = 350)
Age of mothers (years)		
Mean ±SD *(range)*	27.47 ± 5.23 *(19-43)*	
Median (Q1, Q3)	*27 (23.75, 31)*	
Residence	Rural (n, %)	179 (51.1%)
	Urban (n, %)	171 (48.9%)
Education of mother	Primary (n, %)	40 (11.4%)
	Secondary (n, %)	132 (37.7%)
	Graduate (n, %)	162 (46.3%)

	Post graduate (n, %)	16 (4.6%)
Occupational status of the mother	Housewife (n, %)	190 (54.3%)
	Governmental (n, %)	70 (20%)
	Private sector (n, %)	90 (25.7%)
Gravity	Primi (n, %)	174 (49.7%)
	Multi (n, %)	176 (50.3%)
Consanguinity	Positive (n, %)	165 (47.1%)
	Negative (n, %)	185 (52.9%)
Mode of delivery	NVD (n, %)	122 (34.9%)
	CS (n, %)	228 (65.1%)
Place of delivery	General hospital (n, %)	151 (43.1%)
	Private hospital (n, %)	151 (43.1%)
	Private clinic (n, %)	47 (13.4%)
	At home (n, %)	1 (0.3%)

Table (3): Laboratory findings of neonates with jaundice (N=350).

Variable		Statistics
Complete blood count		
WBCs Count $\times 10^3$ /mm		
Mean ±SD *(range)*		13.4 ± 5.2 *(6.2-42)*
Median (Q1, Q3)		*11.95 (9.6, 16.4)*
Hb level (gm/dl)		
Mean ±SD *(range)*		13.5 ± 2.9 (*7.5-22.2)*
Median (Q1, Q3)		*13.2 (11.4, 15.3)*
HCT (%)		
Mean ±SD *(range)*		43.47 ± 7.65 (*29-68)*
Median (Q1, Q3)		*42.1 (38, 48)*
PLT ($\times 10^3$/µl)		
Mean ±SD *(range)*		246.3 ± 64.8 *(45.6-456)*
Median (Q1, Q3)		*240 (197, 298.3)*
Reticulocyte (%)		
Mean ±SD *(range)*		7.67 ± 4.43 *(2-30)*
Median (Q1, Q3)		*6.5 (4.6, 10)*
Liver function		
TSB (mg/dl)		
Mean ±SD *(range)*		19.1 ± 5.14 *(5.1-33)*
Median (Q1, Q3)		*18.7 (15.9, 22)*
Direct bilirubin (mg/dl)		
Mean ±SD *(range)*		1.017 ± 0.609 *(0.2-4.5)*
Median (Q1, Q3)		*0.9 (0.6, 1.3)*
TSB measured at maternity hospital	Yes	82 (23.4%)
	No	268 (76.6%)
Coomb's test	+ve	0 (0%)
	-ve	350 (100%)

The significant jaundice detected in 31.7% of cases, severe jaundice reported in 19.7% of cases, extreme jaundice detected in 14.9% of cases and hazardous hyperbilirubinemia detected in 1.7% of cases .**(table 4)**

Table (4): Categorization of cases according to proposed definition of jaundice severity (N=350).

Level of jaundice	Proposed definition	No. (%) of cases	% of cases
<17 mg/dl	-	112	32%
≥ 17 mg/dl	Significant	111	31.7%
≥20 mg/dl	Severe	69	19.7%
≥25 mg/dl	Extreme	52	14.9%
≥30 mg/dl	Hazardous	6	1.7%

100%t of the studied neonates with jaundice were subjected to intensive phototherapy (capsule therapy). Blood exchange was done in 23.7% and about 36.3% of studied neonates received IVIG infusion. **(table 5)**

Table (5): Ways of treatment (Phototherapy, Blood exchange, IVIG) among the study neonates with jaundice (N=350).

Variable		Statistics
Phototherapy	Single	0 (0%)
	Double	0 (0%)
	Intensive (Capsule)	350 (100%)
Blood exchange	Done	83 (23.7%)
	Not done	267 (76.3%)
IVIG	Given	127 (36.3%)
	Not given	223 (63.7%)

In univariant analysis, older age (hours), higher gestational age, increased birth weight, and increased reticulocyte level were significant positive predictors for increased TSB level ($p<0.05$). On the other hand, decreased hemoglobin level was significant negative predictor for increased TSB level. In the multivariant analysis, it was found that age (hours), gestational age (weeks) and reticulocyte count were significant predictors for increased TSB level ($F= 37.7$, $p=0.000$).**Table 6.**

Table (6): Regression analysis for predictors and risk factors associated with neonatal jaundice (elevated TSB) (n=350).

Variable	Univariate			Multivariate		
	B	95%CI	p	B	95%CI	p
Age of babies (hours)	0.49	0.34-0.50	0.000	0.471	0.033-0.048	0.000
Gestational age(weeks)	0.233	0.442-1.137	0.000	0.129	0.029-0.846	0.036
Birth weight (kg)	0.281	1.653-3.518	0.000			
Reticulocyte count	0.24	0.159-0.397	0.000	0.242	0.174-0.387	0.000
Hb level	-0.186	-0.518-(-0.148)	0.000			

Discussion:

Infants hospitalised with newborn jaundice in this research vary in mean age from 4 to 300 hours. Four-day-old neonates made up the majority of the research. Of the neonates in the research, 48.3% were female and 51.7% were male. Consistent with our findings, the Meslhy research had a male preponderance, with 54.6% of participants being male and 45.4% being female [11]. The proportion closely matched the findings of HennyHarry and Trotman's survey, which found that 39% of the population were female and 61% were male [12]. In 2011 research by Gamaleldin et al., there were 45.8% females and 54.2% men [13]. On the other hand, in a prior cross-sectional analysis, the neonate referral age was between 6 and 8 days of birth, however the majority of patients had jaundice recorded between 2 and 3 days of delivery [14].

The mean gestational age in this research was 36.49 ± 1.52 weeks, with a range of 30 to 40 weeks. The majority of the neonates in the research (34.3%) were 37 weeks gestational age. Mahmoud et al. conducted a prospective cohort study in which the mean gestational age was 37.91±0.77 [15]. The mean gestational age was 38.2 ± 1.4 weeks, according to 2012 research by Iskander et al. [16].

According to the neonates under study, the mean WBC level was 13.4 ± 5.2. The average Hb level in the study group was 13.5 ± 2.9, and the average HCT level was 43.47 ± 7.65. The mean platelet count for the study group was 246.3 ± 64.8. The average number of reticulocytes was 7.67 ± 4.43. Nonetheless, Mahmoud et al. discovered that the jaundice group had 2.64±0.14 times as many reticulocytes as the non-jaundice group. The jaundice group's Hb level was 15.71±0.86, which was comparable to our findings [15].

Only 23.4% of the study neonates had their TSB levels tested in the maternity hospital, and the study group mean TSB level was 5.1-33. According to Meslhy et al., the average total serum bilirubin level at admission was 17.13 ± 3.74 [11].

Mothers in this research are between the ages of 19 and 43 on average. Abbas et al. discovered that there were extremely significant differences ($P<0.01$) between the 54 (72%) women who were under 30 and the 21 (28%), who were over 30 [17].

Approximately 51.1% of the participants in this survey were from rural regions, whereas 48.9% were from urban areas. The majority of mothers (46.3%) had university degrees, whereas 54.3% were housewives who did not work for the government or commercial sector. 0.3% of moms gave birth at home, 13.4% at a private clinic, 43.1% in a private hospital, and 43.1% at a general hospital.

It was discovered that, in the current research, 50.3% of the moms were multigravida, whereas 49.7% were primigravida. Of the study group, 47.1% had positive consanguinity. Abbas et al. also studied mothers of term newborns with neonatal hyperbilirubinemia and discovered that 13 women (17.3%) were primiparous and 62 women (82.7%)

were multiparous, with extremely significant differences between the two groups (P<0.01). [17]. Devi and Vijaykumar disagreed, pointing out that 25.7% of the women were multigravida and 68.6% were primigravida [18].

According to the current survey, over two-thirds of moms (65.1%) gave birth by caesarean section, while 34.9% gave birth vaginally. 0.3% of moms gave birth at home, 13.4% at a private clinic, 43.1% in a private hospital, and 43.1% at a general hospital. According to our findings, the majority of women (64%) in the Abbas et al. research gave birth by caesarean section (C/S), whereas 27 (36%) gave birth vaginally. There were notable disparities between the two delivery methods (P<0.05) [17]. In contrast, Devi and Vijaykumar's prior case control research found that newborn jaundice occurred in 74% of vaginally delivered infants and 25% of caesarean-delivered kids [18].

19.7% of patients (69 out of 350) in the present research had severe jaundice, 14.9% of cases (52 out of 350) had serious hyperbilirubinemia, and 45 out of 350 cases (12.8%) had dangerous hyperbilirubinemia. The majority of patients in our research (44.1%) had severe jaundice due to ABO incompatibility. In 37.8% of instances, Rh incompatibility was the cause. In 18.1% of instances, both Rh and ABO incompatibility were found. Similarly, Bogale et al. found that the primary causes of neonatal jaundice were severe hyperbilirubinemia in 126 (31.6%) of the 399 hospitalised neonates. Jaundice was caused by ABO incompatibility in 35.4% of patients. In 28.3% of instances, Rh incompatibility was the cause. In 6.6% of instances, both Rh and ABO incompatibility were found. Hyperbilirubinemia was the aetiology of jaundice in 29.7% of patients [19].

ABO incompatibility was the most common risk factor for neonatal indirect hyperbilirubinemia (n = 152, 37.6%), according to a cross-sectional study conducted in Bahrain by Isa et al., which also confirmed our findings and hypothesis. The study also found that neonates with ABO incompatibility had a significantly higher mean indirect bilirubin level than those with other risk factors. The most prevalent maternal risk factor, however, was age (>25 years) (n = 331, 81.9%), followed by caesarean birth (n = 137, 33.9%) [20].

Coinciding with the earlier finding, Kumar et al. discovered that the causes of jaundice in the newborns under research were unknown aetiology in 16 (26.6%), ABO incompatibility in 25 (41.6%), and Rh incompatibility in 15 (25%).

In the current investigation, extensive phototherapy (capsule therapy) was administered to almost all of the infants with jaundice. Of the newborns in the study, about 36.3% got IVIG infusion, and 23.7% had blood exchange. According to Meslhy et al., the majority of patients—215 (82.7%)—were treated with intense phototherapy alone, 12 (4.6%) with exchange blood transfusion plus intensive phototherapy, and 32 (12.3%) with intravenous immunoglobulin plus intensive phototherapy [11].

Only 82 out of 350 newborns (23.4%) and 8% of parents who got special instructions or plans for jaundice had their total serum bilirubin levels checked at the maternity hospital. Nearly 58% of parents delayed seeking medical attention because they thought jaundice was a common baby symptom that would go away in time. A severe case of hyperbilirubinemia is caused by all of these conditions.

A very statistically significant positive connection was found in the current research between the TSB level and the following variables: reticulocyte count, birth weight (kg), gestational age (in weeks), and baby age (in hours). Additionally, there is a strong inverse relationship between haemoglobin and TSB levels. Devi and Vijaykumar demonstrated a high correlation (p = 0.0001) between birth weight and hyperbilirubinemia, which is consistent with our findings [18].

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