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HYPERBILIRUBINEMIA;

COMMON HEMOLYTIC CAUSES OF HYPERBILIRUBINEMIA IN FULL TERM NEONATES REQUIRING EXCHANGE TRANSFUSION

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ABSTRACT... Background: Neonatal jaundice is a common condition in the early days of infant's life. It clinically manifests in a significant number of full term babies and almost all premature neonates. Increase in the serum bilirubin during early infancy is multi factorial and may result in kernicterus. Deposition of unconjugated bilirubin in the brain stem nuclei and basal ganglion results in permanent brain damage. **Objective:** To determine the frequency of common hemolytic causes of hyperbilirubinemia in full term neonates requiring exchange transfusion. **Study Design:** Cross-sectional study. **Setting:** Department of Pediatrics, Lady Reading Hospital Peshawar. **Period:** January to June 2015. **Methodology:** A total of 449 full term neonates requiring exchange transfusion were included in this study on the basis of serum bilirubin level (total, direct, indirect). Hemolytic causes were analyzed by checking blood groups, rhesus factors and measuring glucose 6 phosphate dehydrogenase (G6PD) levels. **Results:** In this study mean age was 10 days with standard deviation ± 1.26. Sixty two percent neonates were male and 38% were female. Hemolytic causes were analyzed and ABO incompatibility was found in 25% neonates, rhesus incompatibility in 15% neonates and G6PD deficiency in 32% neonates. **Conclusion:** In this study, the most common cause of severe jaundice requiring exchange transfusion was G6PD deficiency (33%) with hemolysis.

Key words: Exchange Transfusion, G6PD Deficiency, Hemolysis, Hyperbilirubinemia, Kernicterus, Neonatal Jaundice.

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INTRODUCTION

Neonatal hyperbilirubinemia is a clinical condition during early days of infant life which is mostly physiological but higher levels of bilirubin at this age can result in brain damage.[1] It is a common condition in neonates requiring evaluation and has the potential of serious sequale if overlooked. Neonatal jaundice clinically manifest in almost all premature babies and in a significant number of normal neonates.[2] Nearly 5 to 10% of all newborns will need phototherapy for pathological jaundice.[3] Unconjugated bilirubin is deposited in brainstem nuclei and basal ganglia, although it is difficult to predictits exact toxic serum level but kernicterus have been reported in about 1/3 of infants with untreated bilirubin level of more than 25-30mg/dl.[4]

Jaundice results from the raised levels of bilirubin which is a metabolic product of hemoglobin.[5] It is clinically seen by yellow color of skin and sclera and starts appearing on face, spreading in a cephalocaudal manner to abdomen and feet as serum level of bilirubin raises. Blanching the skin with digital pressure may reveal the anatomic progression of jaundice (face=5mg/dl, mid abdomen 15mg/dl, soles20mg/dl).[4,5] It is mostly physiological but pathological jaundice can occur which needs timely detection to prevent kernicterus.[6]

Various pathological conditions can cause neonatal jaundice like isoimmune hemolysis or enzyme deficiency in red blood cells.[7] Prematue breakdown of red blood cells lead to hemolytic jaundice in the form of unconjugated hyperbilirubnemia. Hemolytic disease of new borns is mostly caused by ABO incompatibility

as erythroblastosis fetal is on decline due to use of Rhesus immunoglobulins.[8] In a study ABO incompatibility and Rhesus incompatibility in jaundiced neonates were 22.5% and 12.5% respectively.[9] G6PD deficiency in neonatal period is mostly asymptomatic but can manifest as severe acute hemolysis following exposure to oxidants.[10]

Unconjugated hyperbilirubinemia du to rhesus incompatibility if left untreated can ultimately lead to kernicterus.[11] It is prevented mainly by using intensive phototherapy and exchange transfusions, although exact bilirubin levels at which exchange transfusion is indicated is still controversial.[12] These treatment modalities immediately after birth, not only decreases intravascular clumping but also help in removing the products of excessive hemolysis.[13]

Major causes of neonatal hyperbilirubinemia requiring exchange transfusion are ABO incompatibility, rhesus incompatibility, sepsis, G6PD deficiency and idiopathic.[14]

The aim of this study was to identify the common hemolytic causes of hyperbilirubinemia in neonates, promoting G6PD screening and educating the parents regarding early neonatal visit for timely intervention and thus preventing kernicterus.

METHODOLOGY

This cross-sectional study was done at Department of Pediatrics, Lady Reading Hospital, and Peshawar. The study duration was 6 months from January to June, 2015.

A total of 449 full term neonates in first two weeks of life, with birth weight of more than 2 kg and having clinical and laboratory evidence of indirect hyperbilirubinemia in the range of exchange transfusion were included. Neonates with early signs of kernicterus (lethargy, poor feeding, loss of Moro reflex), preterm neonates before 37 weeks of gestation and neonates with jaundice due to other reasons like sepsis, hypothyroidism etc were excluded.

The study was conducted after approval from hospital ethical and research board. All neonates meeting the inclusion criteria were included in the study through OPD or labor room. All the guardians of the neonates were explained the purpose of procedure, use of data and publication of the study. Informed written consent was taken from them.

The demographic information like name, gender, age and address was recorded. Thorough history was taken and detail physical examination was performed. The baseline routine investigations were done in all neonates. Blood was obtained for blood grouping, serum bilirubin (total, direct and indirect) levels to confirm the presence of jaundice. Blood was taken for checking Rhesus factor, measuring G6PD levels and Osmotic fragility test for hereditary spherocytosis. All the laboratory investigations were done under supervision of expert pathologist having minimum of 5 years experience. The type of treatment was undertaken according to medical ethics, beneficial and not harmful to neonates. All the above mentioned information's were recorded in a pre-designed proforma.

Data collected was analyzed in SPSS Version 12. Mean and standard deviation was computed for numeric variables like age and indirect bilirubin levels. Frequency and percentages were computed for gender and common hemolytic causes (blood group, rhesus factors and G6PD enzyme). Common hemolytic causes were stratified among age, gender and serum bilirubin to see the effect modifiers. All the results were presented in the form of tables and charts.

RESULTS

This study included 449 full term neonates of whom 278(62%) neonates were male and 171(38%) neonates were female with male to female ratio of 1.62: 1 (Table-I).

Ninety (20%) neonates were in age range 1-5 days, 224(50%) neonates were in age range 6-10 days and 135(30%) neonates were in age range 11-14 days. Mean age was 10 days with standard deviation ± 1.26.

Indirect bilirubin level among 449 neonates was analyzed as 112(25%) neonates had bilirubin level ranged 15-20, 283(63%) neonates had bilirubin level ranged 21-25, and 54 (12%) neonates had bilirubin level ranged 26-30. Mean bilirubin was 25 with standard deviation ± 2.75 (Table-II).

Variables	Frequency	Percentage
Age		
1 -5 days	90	20%
6-10 days	224	50%
11 - 14 days	135	30%
Sex		
Male	278	62%
Female	171	38%

Table-I. Various demographic features of cases (n=449)

Serum Bilirubin	Frequency	Percentage
15-20	112	25%
21-25	283	63%
26-30	54	12%
Total	449	100%

Table-II. Indirect bilirubin levels (n=449) Mean bilirubin was 25 with standard deviation ± 2.75

Hemolytic causes among 449 neonates were analyzed and ABO incompatibility was found in 112(25%) neonates, Rhesus factors were positive in 67(15%) neonates and G6PD deficiency was found in 144(32%) neonates (Table-III).

Stratification of Hemolytic causes with age, gender and Indirect bilirubin level are given in Tables-IV,V and VI.

Hemolytic Causes		Frequency	Percentage
ABO Incompatibility:	Yes	112	25%
	No	337	75%
Rhesus Factor	Positive	67	15%
	Negative	382	85%
G6PD Deficiency	Yes	144	32%
	No	305	68%

Table-III. Hemolytic causes (n=449)

Hemolytic Causes		1-5 days	6-10 days	11-14 days	Total	P Value
ABO Incompatibility:	Yes	22	56	34	112	0.002
	No	68	168	101	337	
Rhesus Factor	Positive	13	34	20	67	0.003
	Negative	77	190	115	382	
G6PD Deficiency	Yes	29	72	43	144	0.001
	No	61	152	92	305	

Table-IV. Stratification of hemolytic causes with age (n=449)

Hemolytic Causes		Male	Female	Total	P Value
ABO Incompatibility:	Yes	69	43	112	0.002
	No	209	128	337	
Rhesus Factor	Positive	42	45	67	0.002
	Negative	236	126	382	
G6PD Deficiency	Yes	89	55	144	0.002
	No	189	116	305	

Table-V. Stratification of hemolytic causes with gender (n=449)

Hemolytic Causes		15-20	21-25	26-30	Total	P Value
ABO Incompatibility:	Yes	28	71	13	112	0.001
	No	84	212	41	337	
Rhesus Factor	Positive	17	42	8	67	0.003
	Negative	95	279	46	382	
G6PD Deficiency	Yes	36	91	17	144	0.003
	No	76	192	37	305	

Table-VI. Stratification of hemolytic causes with indirect bilirubin levels (n=449)

DISCUSSION

Exchange transfusion is currently the most effective treatment for neonates with severe jaundice. Although in recent years the number of neonates requiring exchange transfusion has decreased, approximately 7% of neonates still need this procedure.[15]

Our study shows that mean age was 10 days with standard deviation ± 1.26. Sixty two percent neonates were male and 38% neonates were female. Hemolytic causes were analyzed and ABO incompatibility was found in 25% neonates, rhesus factors were positive in 15% neonates and G6PD deficiency was found in 32% neonates. Different rates were reported by Koosha et al[16] and Behjati et al[17] from Iran, who reported exchange transfusion rates of 3.7% and 14.4% respectively.

Differences in the exchange transfusion to admission ratio may be due to different causes of jaundice and delays in referral to medical centers. Delay in referral to medical center may be due to limited experience of general physicians providing primary care in rural areas, and incorrect knowledge of parents about treatment of hyperbilirubinemia.[18]

In another study, the most common cause of severe jaundice leading to exchange transfusion was 'undetermined' (38.9%), which may due to the fact that we have limited diagnostic facilities to identify various causes of pathologic jaundice, Sanpavat et al[18] from Thailand and Chen et al[19] from Taiwan. Unlike our findings, however, the most common causes leading to exchange transfusion reported by Badiee[20] from the Islamic Republic of Iran, Abu-Ekteish[21] from Jordan and Steiner et al[22] from the United States were ABO incompatibility, G6PD deficiency and Rhesus incompatibility, respectively. This difference maybe due to difference in pattern of these hematologic abnormalities. G6PD deficiency is a genetic disorder that may be present in the higher percentage in our province than other places. But there is not much published research in this field this is only a hypothesis which is supported by daily observation.

The trend to reduce the length of hospital stay for both mothers and infants after birth has resulted in rising readmission rates dues to severe jaundice. Therefore, it must be emphasized that neonates at risk of severe jaundice should be evaluated before discharge and their bilirubin levels measured. In this study, most cases of exchange transfusion (67, 51.1%) were done between 2 and 4 days after birth, and the mean age of the neonates at the time of exchange transfusion was 4.2 days. In our country due to economic constraints and lack of support provided by insurance organization, most of the new borns discharged from hospital even earlier than 24 hr.[23]

Badiee'study[20] reported a mean age of 4.4 days, indicating early referral and timely exchange transfusion in these neonates. In our study, 70.9%of neonates who underwent exchange transfusion were full term. A similar finding was reported by the Sanpavat's study (72.9%).[18]

G6PD deficiency is the most common X-linked enzyme deficiency disease throughout the world. Deficiency of this enzyme is a major cause of severe jaundice and can lead to kernicterus and death.[23] According to a World Health Organization (WHO) report, the Islamic Republic of Iran is located in an area with an average-to high prevalence of G6PD deficiency.[24] Previous studies in Iran have shown that the prevalence of this enzyme deficiency is greater in the north and south than in other provinces. In one study, 33% of neonates who underwent exchange transfusion had G6PD deficiency. In contrast, the rate of enzyme deficiency in neonates who underwent exchange transfusion was from Thailand[17], 13.4% in Sanpavat et al,[18] 17% in the study by Chen et al from Taiwan[19] and 19% in the Badiee study from Iran.[20] Nevertheless, the rate of enzyme deficiency reported by Abu-Ekteish et al[21] from Jordan was 38%.

The male to female ratio in all neonates who underwent exchange transfusion in the present study was 1.62:1; in cases with enzyme deficiency, the ratio was 3.8:1. This finding is similar to that of the study by Sharma et al[25] who reported a male to female ratio of 1.3:1 among

neonates with jaundice. It is also similar to the results of studies by Ahmadi et al[26] and Eghbalian et al[27] who reported a male to female ratio of 3:1 and 5:1among enzyme-deficient neonates, respectively.

The gene responsible for G6PD deficiency has X linked transmission, so the disease occurs only in hemi zygotic males and homozygotic females. Inactivation of an X chromosome may lead to the appearance of two groups of RBCs in heterozygotic females. In such cases, the patient's RBC may exhibit normal, average or overtly decreased enzyme activity.[22] The necessity to repeat exchange transfusion in male neonates indicates a more severe enzyme deficiency in males than in females, indicating that all hemizygotic males and homozygotic or heterozygotic female neonates harbor inactive X chromosomes.

In another study, in 80% of cases, jaundice appeared in neonates with enzyme deficiency on the 2nd or 3rd day after birth, and the mean age at the time of exchange transfusion in neonates with enzyme deficiency was younger than that in neonates with normal enzymes. However, this observation is not in agreement with the report by Bhutani[28] in which jaundice was noted to appear in most patients with enzyme deficiency on the 1st day after birth. This difference may is due to referral bias and early discharge of new borns in our region, which in vaginal delivery cases is ≤ 24-hour and in caesarean section delivery cases is between 24 to 48-hour post delivery. Furthermore, missing of screening test for G6PD in umbilical cord blood that lead to misdiagnose of at risk new borns is also a cause for this difference.

Our findings showed no significant difference in mean bilirubin levels and haemoglobin levels between the normal enzyme-activity andenzyme-deficiency groups. Similar findings were reported by Ahmadi et al[26] indicating that hemolysis is not the cause of jaundice in these neonates. Possibly, a concurrent gene mutation in G6PD activity and errors in uridine diphosphateglucose utilization are the possible causes of this problem.[29] Factors leading to hemolysis in neonates with enzyme deficiency include infection, acidosis, hypoglycemia, oxidant drug and/or fava bean usage by the mother and oxytocin injection at delivery as showed by Eghbalian et al[27] but discordant with a study by Madan et al[30] that reported hemolysis in 10.9% and 41.7%, respectively, of neonates with enzyme deficiency. WHO recommends a G6PD screening for all neonates born in high-prevalence (3%–5%) areas, including Iran.[20] In cases that underwent exchange transfusion, G6PD was the most common identified cause.

CONCLUSION

It is concluded on the basis of this study that G6PD enzyme deficiency is the most common hematologic factor among neonates who underwent exchange transfusion as a result of hyperbilirubinemia. Gene mutation analysis may be appropriate to determine which type is the predominant. Moreover, early detection of G6PD enzyme deficiency is essential to prevent neonatal hyperbilirubinemia and consequently kernicterus in future.

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Giving someone the power to destroy you, and trusting them not to.

– Unknown –

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Mohsin Hayat	Discussion and references.	
2	Mohammad Irshad	Methodology and resutls.	
3	WajehaTaj	Data collection and introduction.	
4	Ihsan Ullah	Overall supervision ans pathologist, review of the article and final correction.	
5	Amir Mohammad	Abstract.	
6	Afzal Khan Khatak	Tables and conclusion.	