ORIGINAL ARTICLE

A Study of Various Causes of Indirect Hyperbilirubinemia in Neonates

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ABSTRACT

Background: Neonatal jaundice is a fairly common cause of morbidity in Pakistan and accounts for almost 25% of all newborn admissions[(1]. This may also account for the wide variation in the etiology of jaundice from various reports in Pakistan.

Aim: To describe the etiology hemolytic jaundice in the region of Bahawalpur, Pakistan and to identify factors determining the severity of hyperbilirubinemia.

Methods: sixty cases of jaundice were ad mitted in various units of BV Hospital/QAMC Bahawalpur referred from various DHQ hospitals of Bahawalpur Division. They were examined clinically and were investigated hematologically to be differentiated from other groups of jaundice by various routine and special tests like blood count, enzyme assay, RBC fragility and coomb's test etc

Results: Sixty neonates referred to various units of Bahwal Victoria Hospital, Bahawalpur during the period of 1 year were investigated for this purpose. 22(36.6%) out of 60 cases of hemolytic jaundice were found to showed exaggerated physiological jaundice, 2(3.3%) from G6PD enzyme deficiency, 4 (6.6%) were diagnosed as a case of hereditary spherocytosis, 8(13%) were of ABO incompatibility, 10(16.6%) infections 5(8.3%) of drug induced hemolytic anemia.

Conclusion: It is observed that indirect hyperbilirubinemia may be associated with a wide variety of disease states like cardiac, GI disorders, infections and due to increased pigment production. Incidence of hemolytic anemia due to G6PD deficiency needs further probing to evaluate the incidence of this disorder in the population of Bahawalpur Division initially and then in population of Pakistan after collecting data from other areas of the country.

Keywords: Indirect hyperbilirubinemia, Jaundice, G6PD, Infections. NH: neonatal hyperbilirubinemia

INTRODUCTION

Increase rate of hemoglobin degradation in hemolytic anemia, congenital and acquired, will lead to increased bilirubin concentration in blood stream. Liver may not be able to properly excrete the greater load of pigment present, and this increased bilirubin level will result in the clinical condition of jaundice (hemolytic or prehepatic). It is important to determine the cause of indirect hyperbilirubinemia so proper treatment can be directed. Hemolysis is of two types; 1) Intravascular , caused by rupture of red cells within the blood stream. 2) Extravascular, removal of red cells from the blood stream by cells of reticuloendothelial system. Most hemolysis occurs extravascularly i.e. by the phagocytic cells in spleen, liver and bone marrow. Hemolysis is usually due to 1. Abnormalities within RBCs (Hemoglobin or metabolism); 2) abnormalities of RBC membrane (permeability, structure, or lipid content) or 3) abnormalities extrinsic to RBC (serum antibodies, trauma in circulation or infectious agents). It can be seen in all age groups. Causes also vary in various age groups. Most cases of neonatal hyperbilirubinemia are due to physiological jaundice and go without have serious consequences. The important challenge clinically is to identify those newborns that may develop severe neonatal hyperbilirubinemia[1]. There are many factors involved in the development of pathological jaundice, which may include perinatal factors (e.g., birth trauma or infections), maternal factors(e.g., Rh or ABO incompatibility), neonatal factors (e.g., prematurity or polycythemia), and genetic factors (e.g., Crigler-Najjar's or Gilbert's syndrome)[2]. The administrations of drugs like cephalosporins and glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency have been implicated in pathological jaundice[2]. The mechanism of hyperbilirubinemia is through either increased production of bilirubin (resulting from hemolysis, sepsis, blood extravasation or polycythemia) or increased enterohepatic circulation (resulting from prematurity, pyloric stenosis, delayed bacterial gut colonization, gastrointestinal tract immobility or obstruction), or a decrease in bilirubin elimination which occurs in Crigler-Najjar's and Gilbert's syndromes[2]

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ABO incompatibility is usually found in the offsprings of women with blood type O and on occasions in mothers with both type A blood and having high anti-B IgG levels[3]. ABO incompatibility may exist in approximately 15–25% of all maternal/fetal pairs. However, ABO hemolytic disease of the newborn is found in approximately 1% of group O mothers who carry a high antenatal IgG antibody titers[4]. At present, with the use of prophylactic anti-D immunoglobulin has greatly reduced the incidence of hemolytic disease of the newborn resulting from Rh incompatibility[5].

G6PD deficiency is an X-linked recessive disease resulting in clinical manifestations such as neonatal jaundice, chronic nonspherocytic anemia, infections and drug-induced hemolysis[6]. G6PD deficiency has been reported to be involved in the genesis of neonatal hyperbilirubinemia[7]. One of the most serious complication of G6PD deficiency seen in newborns is kernicterus resulting from severe neonatal hyperbilirubinemia. Those infants who suffer from chronic or acute fetal hypoxia have a higher risk of polycythemia, with hematocrit levels greater than 65% and have neonatal hyperbilirubinemia as a common clinical feature[8].

Hyperbilirubinemia may also be a result of increased oxidative stress. It is reported that bilirubin also functions as a scavenger of reactive oxygen species[9]. Malondialdehyde (MDA) is a reactive metabolic product that results from the effects of reactive oxygen species on tissues and from a series of reactions that occur during lipid peroxidation[10].

MATERIALS AND METHODS

Investigations were carried out in all cases of significant jaundice, which included maternal and neonatal blood groups, serial levels of total serum bilirubin, direct bilirubin, Coombs test, hemoglobin and hematocrit, reticulocyte count, and peripheral blood smear. G6PD deficiency was screened in red cells by a qualitative, visual colorimetric method using dichlorophenol as dye. An 'Infection' being a cause of jaundice in newborn infants was ascribed to those with positive blood cultures and/or features of infection necessitating antibiotics for ≥ 7 days, in the absence of any other attributable cause for jaundice. Data was analyzed using SPSS version 6.1.

RESULTS

Table 1: Clinical and laboratory data

	G6PD DEF	**Exaggerated Physio-logical**	**Abo Incompatbility**	**Hereditary Spherpcytosis**	**Rh Incompati-bility**	**Drug induced**	**Bacterial toxins**
Anemia	+	+ --	++	++	++	+++	+++
Jaundice	+	++	+	+	+++	+	++
Splenomegaly	+	--	++	++	++	+ --	+
Hepatomegaly	--	--	+ --	+ --	++	--	+
Fever	+ --	--	--	--	+	+	+++
Coombs test	-	--	-	-	-	++	-
Reticulocytosis	5-10 %	--	10-12%	4-8%	15-20%	5-8%	15-20%
Abnormal morphology	Anisopoikilocytosis like broken egg shells ++	Anisopoikilo-cytosis	Anisopoikilo-cytosis	Spherocytes	Sphero-cytes	Anisopoikilocytosis	Anisopoikilocytosis
Urobilinogen	Increased	+	Increased	Increased	Increased	Increased	Increased
Enzyme	G6pd def	N	N	N	N	N	N

Table 2: Gender distribution of hemolytic anemia

Gender	**n**	**%age**
Male	38	63.3
Female	22	46.6

Table 3 : Causes of hemolyitic anemia in neonates

Cause of hemolytic anemia	**n**	**%age**	**Male**	**%age**	**Female**	**%age**
G6pd deficiency	2	3.3	2	100	0	0
Hereditary spherocytosis	4	6.6	4	100	0	0%
Rh incompatibility	9	15	5	55.5	4	44.4
Abo incompatibility	8	13	3	37.5	5	62.5
Infections	10	16.6	4	40	6	60
Drug induced	5	8.3	4	85.7	1	14.2
Exaggerated physiological	22	36.6	18	81	4	18.8

DISCUSSION

Neonatal hyperbilirubinemia is associated with a variety of conditions. Severe NH poses a direct risk of permanent neurological sequelae. Therefore, early recognition of neonates who are at a higher risk of developing severe neonatal hyperbilirubinemia is of paramount importance to preventing brain damage[17]. In our study, physiological jaundice is found to be the most frequent cause of neonatal jaundice 36%. These findings are comparable to various national and international studies[18,19]. Physiological aspects that can lead to neonatal hyperbilirubinemia include increased bilirubin production, less efficient hepatic conjugation, and increased bilirubin absorption by the enterohepatic circulation[20]. Bilirubin has been an effective antioxidant, and modest elevations of bilirubin may be beneficial in neonates[21].

ABO incompatibility and G6PD deficiency were found to be frequent causes of neonatal hyperbilirubinemia in our study, as well as in other studies. The deficiency of G6PD is the one of most common human genetic enzymopathy, affecting over 200 million individuals worldwide. It has been associated with neonatal jaundice, chronic nonspherocytic hemolytic anemia, favism and food- or drug-induced acute hemolytic anemia[22].

In majority of cases, ABO hemolytic disease of newborns causes hyperbilirubinemia without severe neonatal anemia, which is due to few group A or B antigens on neonatal red blood cells and the presence of A and B antigens on other tissues and in body fluids[24]. This fact is also revealed in our study, as most ABO incompatible cases had normal hemoglobin levels. In the indirect hyperbilirubinemia group, Rh hemolytic disease of the newborns is in agreement with previous studies, that depicted that Rh hemolytic disease of the newborn is less common than previously due to the administration of Rh Ig, which results in a greater than 90% reduction in the alloimmunization rate among treated women[30,31].Our data highlight the importance of drugs, infection and ABO and Rh incompatibility in newborns with significant jaundice in Bahawalpur and also of G6PD deficiency in this study. Due to lack of sophisticated laboratory facilities, we were unable to further analyze the subcategory of miscellaneous hemolyses to determine specific etiologies. Multiple etiologies are found to operate in several newborns, *e.g.,* infection and prematurity whereas we primarily ascribed physiological jaundice as the dominant etiology in our analysis. Infection (16%) was the second most common etiology, it was still less than a figure of 53% previously reported from Pakistan[1]. This is probably because of the selective nature of previously reported case series. While the rate of infection is much lower than in Africa[17] and comparable to data from the Middle East and India.[18,19]. It still remains much higher than developed countries, where sepsis accounts for less than 5% of significant hyperbilirubinemia[20,21] . This indicates the need for aggressively treating infection associated with jaundice.

Hemolytic jaundice accounted for almost 20% of all significant jaundice, with ABO and Rh incompatibility contribute to two thirds of the total. ABO incompatibility is usually reported as a milder disease in comparison to Rh disease,[22] However newborns with ABO incompatibility in our series had more severe hemolysis with significantly higher bilirubin and lower hemoglobin levels which is similar to previous Pakistani reports [12 23] and support the contention that ABO incompatibility is a severe disease in South Asia[24]. While studies from northern Pakistan (predominantly Pathan ethnicity) reports a 7-8% prevalence of G6PD, deficiency[13,25]. Our results from Bahawalpur, a multiethnic city in the Southern Punjab region of Pakistan reveal a figure of 3%. This is comparable to reports from Singapore, and Malaysia[26,27] although less than reports from the Middle East[28] and India[29] However, all cases of G6PD deficiency had evidence of severe hemolysis. Despite this low prevalence, given that G6PD deficiency has hemolytic jaundice with comparable severity to ABO and Rh incompatibility, we would recommend a qualitative G6PD deficiency test in all Pakistani newborns with suspected hemolysis.

CONCLUSION

In summary, our data from this study done in Bahawalpur reveals prevalence of significant jaundice of which a fifth were attributable to hemolytic causes. Infection accounted for a large proportion (16%) of all cases and in 36% labeled as exaggerated physiological jaundice. ABO and Rh isoimmunization, G6PD deficiency and sepsis were independent risk factors for severe jaundice.

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