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Pattern of glucose 6 phosphate dehydrogenase deficiency in neonates with hyperbilirubinemia in a tertiary care center

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Abstract
Background: G6PD deficiency leading to neonatal hyperbilirubinemia is not an uncommon disorder in India. However it is highly under diagnosed and poorly reported.
Method: In this retrospective study, data of 108 neonates treated for neonatal hyperbilirubinemia and also screened for G6PD deficiency in the neonatal unit of MGM Medical College, Kishanganj, Bihar and Medica North Bengal Clinic, Siliguri, West Bengal during the period January 2016 to December 2016 were analysed and taken up for the study.
Results: Out of 108 neonates who were screened for G6PD deficiency, 11.1 1% were found to be deficient with a male predominance. Bilirubin encephalopathy was seen in 6 babies. ABO incompatibility was the most common cause of neonatal hyperbilirubinemia.
Conclusion: Screening for G6PD deficiency routinely in all cases of neonatal hyperbilirubinemia or at least in cases where more common causes are ruled out could go a long way in preventing lifelong consequences of bilirubin toxicity and reducing the burden of handicapped children to the parents and the society at large.

Keywords: hyperbilirubinemia, MGM, LSK

1. Introduction
Jaundice is observed in more than 80% of all healthy new newborns during the first week after birth [1, 2]. Although this condition must have been noticed by caregivers throughout the centuries but the first scientific description of neonatal jaundice was made by Baumes in later part of the 18th century in Paris. Although most jaundiced infants are otherwise perfectly healthy, they make us anxious because bilirubin is potentially toxic to the central nervous system [3]. Hyperbilirubinemia may cause bilirubin encephalopathy with disastrous consequences in some infants.
In day to day clinical practice in India in addition to history taking and clinical examination, a neonate with neonatal jaundice is commonly subjected to the following lab investigations: hemoglobin, sepsis screening, blood group including mothers and serum bilirubin with fractions. However hyperbilirubinemia in newborn period can be associated with severe illness such as hemolytic disease, metabolic and endocrine disorders, anatomic abnormalities of the liver and infections.
Glucose 6 phosphate dehydrogenase deficiency is the most frequent human enzyme defect estimated in approximately 400 million individuals worldwide [4, 5]. The incidence of neonatal jaundice is several folds higher in G6PD deficient infants compared with those who are sufficient [6].
This study was conducted primarily to highlight the importance of G6PD in all jaundiced neonates to facilitate early diagnosis and prevent long term morbidity.

2. Method
This is a retrospective study conducted in MGM Medical College and LSK Hospital Kishanganj, Bihar and Medica North Bengal clinic, Siliguri, West Bengal. The data were collected from record sections of the two centers. In our study we have included only those cases who were hospitalized for the treatment of hyperbilirubinemia with bilirubin level ≥14 mg/dl in case of term babies and ≥12 mg/dl in case of preterm babies and each one of them screened for G6PD deficiency during the period January 2016 to December 2016.
All the vital information like history, physical examination laboratory data and those requiring phototherapy and/or exchange transfusion were collected from the records and were analysed thoroughly.
From the medical record each file was studied for birth weight, age at the time of presentation, gestational age, G6PD status, total bilirubin including direct and indirect, blood group and Rh typing of baby and mother, CRP, Hb, TC, DC (sepsis screening), TSH, presence of cephalhematoma and reticulocyte count.

3. Results
In this retrospective study involving 108 neonates who were hospitalised with hyperbilirubinemia and were screened for G6PD deficiency during the period January 2016 to December 2016, 62 (57.41%) were male and 46 (42.55%) were female.
Eight (7.4%) babies were large for gestational age, 66 (61.1%) were appropriate for gestational age whereas 34 (31.5%) neonates were small for their gestational age.
Among the 108 neonates 87 (80.6%) neonates were term

babies whereas 21 (19.4%) were preterm. Out of the 87 full term babies 49 had bilirubin level between 14 to 17 mg/dl, 35 had bilirubin level between >17 to 20 mg/dl, one neonates had bilirubin level between >20-25 mg/dl and 2 babies had bilirubin levels more than 25 mg/dl. There were 21 preterm babies out of which 12 babies had bilirubin level between 12 to 17 mg/dl, 6 babies had bilirubin level between >17 to 20 mg/dl whereas 2 babies had bilirubin level >20 – 25 mg/dl and one baby had bilirubin level >25 mg/dl.

The age at the time of presentation was less than 3 days in case of 8 (7.4%) whereas 69 (63.9%) neonates presented between day 3 to day 7 and 31 (28.7%) neonates presented after 7 days of age.

Among the various causes of hyperbilirubinemia ABO incompatibility was found to be the most common cause. In our study 26 (24.07%) neonates had hyperbilirubinemia due to ABO incompatibility. Sixteen (61.54%) were male and 10 (38.46%) were female.

In 22 babies, the cause of hyperbilirubinemia was not known - 12 (54.55%) among them were male and 10 (45.45%) were female. Out of 17 premature babies who had hyperbilirubinemia, 9 (52.94%) were male and 8 (47.06 %) were female. In our study 10 (9.26%) neonates with hyperbilirubinemia had sepsis with equal male and female distribution. Rh incompatibility was seen in 9 (8.33%) babies among whom 4 (44.4%) were male and 5 (55.6%) were female.G6PD deficiency was seen in 12 (11.11%) babies with male predominance: where 9 (75%) were male and 3 (25%) were female. Out of these 12 babies all had serum bilirubin level approaching or beyond 20 mg/dl.

Other causes of hyperbilirubinemia in our study were as follows: Breast milk jaundice 6 (5.56%), cephalhematoma 3 (2.78 %), hypothyroidism 2 (1.8 5%) and polycythemia 1 (0.9 3%).

In case of breast milk jaundice gender distribution was equal that is 3 male and 3 female babies. In case of cephalhematoma 2 neonates were male and one was female whereas in case of hypothyroidism both the babies were male. One female baby had polycythemia.

Kernicterus was found in 6 babies, out of which 5 were male and 1 was female and among them 4 were G6PD deficient and one each had Rh incompatibility and ABO incompatibility. The latter two were home delivered.

All the babies were given double surface phototherapy covering the eyes and genitalia. Exchange transfusion was necessary in 10 cases.

4. Discussion

Our study involved 108 neonates who were treated for neonatal hyperbilirubinemia with varied etiology. All of them were subjected to screening for glucose 6 phosphate dehydrogenase deficiency. The most common cause of hyperbilirubinemia was ABO incompatibility followed by idiopathic, prematurity, G6PD deficiency, sepsis, Rh incompatibility, breast milk jaundice, cephalhematoma, hypothyroidism and polycythemia. Similar observations with regard to etiology was seen in several studies [7, 8].

Although glucose 6 phosphate dehydrogenase deficiency was not amongst the most common causes of hyperbilirubinemia, this study was undertaken primarily because of the fact that there is no study on G6PD deficiency and hyperbilirubinemia in a region of eastern Bihar and adjoining North Bengal.

Hyperbilirubinemia in newborn with glucose 6 phosphate dehydrogenase deficiency is a serious clinical problem because of the severity and unpredictability of its course (9). It has been observed that G6PD deficiency neonates are at increased risk for hyperbilirubinemia even in the nursery, free from agent that can potentially cause haemolysis to G6PD deficiency red cells [10].

Jaundice in G6PD deficient neonates is considered to be due to an imbalance between the production and conjugation of bilirubin, with a tendency for inefficient bilirubin conjugation. Borderline premature infants are at special risk of the bilirubin production conjugation imbalance [11].

G6PD deficiency is an X-linked disease that primarily affects men. Women may be affected if they are homozygous, which occurs in populations in which the frequency of G6PD deficiency is quite high. Heterozygous women (carriers) can experience clinical disease as a result of X- chromosome inactivation, gene mosaicism or hemizygosity [12]. In our study too, there was male preponderance with 9 male and 3 female who has G6PD deficiency.

G6PD deficiency can lead to an increased risk and early onset of hyperbilirubinemia [13, 14] which may require phototherapy or exchange transfusion [4, 14]. In certain population hyperbilirubinemia secondary to G6PD deficiency results in an increased risk of kernicterus and death [15, 16]. Whereas in other populations this has not been observed [17]. This may reflect genetic mutations specific to different ethnic groups [17, 18].

The highest prevalence of G6PD deficiency is reported in Africa, Southern Europe, The Middle East, Southeast Asia and the central and Southern Pacific Islands; however G6PD deficiency has now migrated to become a worldwide disease [19].

Deficiency of this enzyme was reported from India more than 50 years back. The prevalence varies from 2.3 to 27% with an overall prevalence of 7.7% in different tribal group [20]. A study by Bisoi *et al* reported G6PD deficiency in 14.68% of live newborns in Kolkata, West Bengal [21]. In our study, out of 108 neonates 12 babies 11.1 1% were deficient in G6PD.

Since the subject evaluated in our study belonged to a mixed population including Bengali, Bihari, Surjapuris, Adivasi, Gorkhas, Koch Rajbanshi etc of Eastern Bihar and adjoining North Bengal practicing Hinduism, Islam, Buddhism and Christianity, commenting on their ethnicity and tribal status is beyond the scope of this study.

In a study by Vandana Rai and Pradeep Kumar [22], G6PD deficiency in Muslim community of Junapur district of Uttar Pradesh was 13%. Similar data were reported from Muslim populations of other neighboring Asian countries: Bangladesh 3.3 to 20% [23], Pakistan 1.07 to 3.17% [24], Malaysia 3.3 to 17% [25] and Indonesia 2.7 to 17.5% [26].

In the US Pilot Kernicterus Registry, 20.8% of newborns cared for as healthy infants readmitted within a week of discharge with acute bilirubin encephalopathy were subsequently diagnosed to have G6PD deficiency [27]. Similar findings from a survey from the United Kingdom and Ireland reported hundred and eight newborns with extreme neonatal hyperbilirubinemia (30 mg/dl) in whom G6PD deficiency

independently increased the risk of encephalopathy many fold [28].

In our study 6 babies had presented with or developed features of bilirubin encephalopathy with 4 of them being G6PD deficient. Exchange transfusion was necessary in 10 babies.

5. Conclusion

G6PD deficiency leading to neonatal hyperbilirubinemia is not an uncommon disorder in India as seen from several publications. Delay in recognition can lead to rapid progression of severe hyperbilirubinemia and consequent bilirubin induced neurological damage. However due to lack of parental awareness about G6PD deficiency and an ongoing practice among clinicians of 'not including' G6PD screening routinely in jaundiced neonates, the condition is highly under diagnosed and poorly reported with negligible research in this field in our country. Screening of all neonates with neonatal jaundice for G6PD deficiency would be ideal. However lack of facilities in all centers coupled with financial constraints are likely to play spoilsport. So screening for G6PD deficiency could perhaps be done routinely in all those cases in which other more common causes are ruled out. This step alone could go a long way in preventing lifelong consequences of bilirubin toxicity and reducing the burden of handicapped children to the parents and society at large.

Table 1: Gender distribution in neonates with hyperbilirubinemia

Gender	No of Neonates	
	N = 108	(%)
Male	62	57.41%
Female	46	42.59%

Fig 1: Pie diagram showing gender distribution in neonates with hyperbilirubinemia.

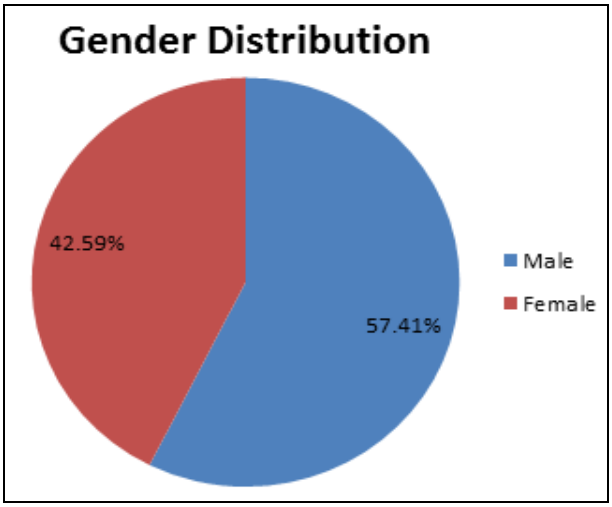

Table 2: Serum bilirubin levels in Term and Preterm Neonates

Full Term Neonates		Pre Term Neonates	
87 (80.6%)		21 (19.4%)	
Serum Bilirubin	No of neonates	Serum Bilirubin	No of neonates
14 – 17 mg/dl	49	12 – 17 mg/dl	12
> 17 – 20 mg/dl	35	>17 – 20 mg/dl	6
> 20 – 25 mg/dl	1	> 20 - 25 mg/dl	2
>25 mg/dl	2	>25 mg/dl	1

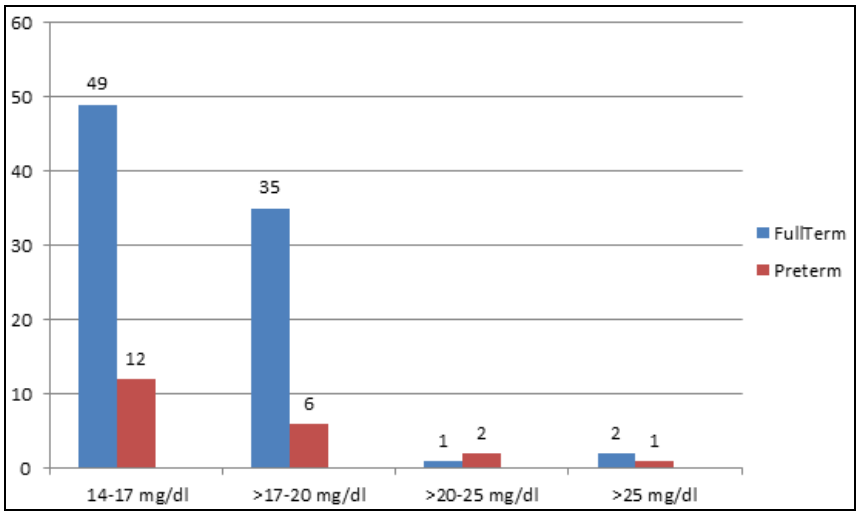

Fig 2: Bar diagram showing serum bilirubin levels in term and preterm neonates.

Table 3: Birth weight and age at the time of presationation.

Birth Weight		Age at the time of presentation	
Weight	No of neonates with percentage	Age	No of neonates with percentage
LGA	8 (7.4%)	<3 days	8 (7.4%)
AGA	66 (66.1%)	3 – 7 days	69 (63.9%)
SGA	34 (31.5%)	>7 days	31 (28.7%)

Table 4: Causes of Neonatal Hyperbilirubinemia

Various Causes	No of Neonates with Percentage		Male babies No with Percentage		Female babies No with Percentage	
ABO incompatibility	26	24.07%	16	61.54%	10	38.46%
Idiopathic	22	20.37%	12	54.55%	10	45.45%
Prematurity	17	15.74%	9	52.94%	8	47.06%
G6PD Deficiency	12	11.11%	9	75%	3	25%
Sepsis	10	9.26%	5	50%	5	50%
Rh incompatibility	9	8.33%	4	44.4%	5	55.6%
Breast Milk Jaundice	6	5.56%	3	50%	3	50%
Cephalhematoma	3	2.78%	2	66.67%	1	33.33%
Hypothyroidism	2	1.85%	2	100%	0	0%
Polycythemia	1	0.93%	0	0%	1	100%

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