Clinical and Biochemical Profile of Neonates with Hyperbilirubinemia in a Tertiary Care Center

Authors

Dr Niru Chhetri¹, Dr Ajit Chhetri²

¹Associate Professor in Biochemistry, MGM Medical College and LSK Hospital, Kishanganj, Bihar
²Senior Consultant Pediatrician and Neonatologist, Medical North Bengal Clinic, Siliguri, West Bengal

Corresponding Author

Dr Niru Chhetri
Associate Professor in Biochemistry, MGM Medical College and LSK Hospital, Kishanganj, Bihar
Email: niruchhetri@ymail.com

ABSTRACT

Background: Neonatal hyperbilirubinemia, though of common occurrence, is a significant medical condition not only because of its impact on hospital discharge but more importantly because of its potential to cause serious long term neurological complications.

Method: In this retrospective study, data of 258 neonates treated for neonatal hyperbilirubinemia in the neonatal unit of MGM Medical College, Kishanganj, Bihar during the period January 2016 to December 2016 were analyzed and taken up for the study.

Results: In our study ABO incompatibility was the most common cause of neonatal hyperbilirubinemia followed by idiopathic, prematurity, Rh incompatibility and glucose 6 phosphate dehydrogenase deficiency, in addition to other minor causes. Male preponderance was seen. Unfortunately bilirubin encephalopathy (Kernicterus) was seen in a couple of cases.

Conclusion: ABO incompatibility is a very common cause of neonatal hyperbilirubinemia. Although historically Rh incompatibility has been accorded much importance, ABO incompatibility should alert the attending doctors about the impending risk of significant neonatal jaundice. If discharged early a written protocol should be followed where a revisit should be planned within 1 to 3 days for babies with any risk factor so that hyperbilirubinemia, if any, is detected and treated accordingly to prevent long term neurological morbidity.

Key Words: Neonates, Hyperbilirubinemia, ABO incompatibility, Prematurity, Jaundice, G6PD.

INTRODUCTION

Neonatal jaundice is observed during the first week of life in 60% of full term infants and 80% of preterm infants¹. It is one of the most common causes of readmission in neonates and also a case of ‘LAMA – Left Against Medical Advice’ because of delay in discharge.

Neonatal Jaundice is broadly classified as physiologic and non physiologic hyperbilirubinemia; in the former the level rises to 6 to 8 mg/dl by 3-5 days of age and may reach up to 12 mg/dl and then falls. Non physiologic hyperbilirubinemia is one in which onset of jaundice is before 24 hours of age or persists beyond 8 days. In fact any elevation of serum bilirubin that requires phototherapy is non physiologic.² This study was conducted to know the profile of neonatal hyperbilirubinemia in babies admitted in a
tertiary care hospital in Bihar, India. Although there are innumerable studies on neonatal jaundice worldwide, there are hardly any studies from this region.

MATERIALS AND METHODS
This retrospective study was conducted in MGM Medical College and LSK Hospital, Kishanganj, Bihar. The data was collected from the medical record section of the college.

A total of two hundred and fifty eight neonates were taken up for the study. Those babies who were admitted in the neonatal unit (NICU) during the period January 2016 to December 2016 for the treatment of hyperbilirubinemia with bilirubin level of ≥14 mg/dl in case of term babies and ≥12 mg/dl in case of preterm babies were considered for the study.

All other details like history, physical examination, laboratory tests and those requiring phototherapy and/or exchange transfusion, were collected from the medical records and were thoroughly analyzed. Details of laboratory investigation done which included – total bilirubin (conjugated and unconjugated bilirubin), blood group of mother and neonate, Hb, TC, DC, and CRP (sepsis screening), G6PD status, TSH levels were collected and analyzed in our study.

RESULTS
After thoroughly analyzing the data, a total of 258 neonates with hyperbilirubinemia – with bilirubin level ≥ 14 mg/dl in case of term babies and ≥12 mg/dl in case of preterm babies were included in the study. It was seen that out of 258 neonates 144 (55.8%) were male and 114 (44.2%) were female and 195 (75.58%) were full term babies whereas 63 (24.42%) were preterm babies. (Table 1)

Out of 195 full term babies 109 (55.90%) had bilirubin level between 14 to 17 mg/dl, 67 (34.36%) had bilirubin level between >17 to 20 mg/dl whereas 19 (9.74%) neonates had bilirubin level more than 20 mg/dl.

Amongst the 63 preterm babies 31 (49.21%) had bilirubin level between 12 to 15 mg/dl whereas 25 (39.68 %) babies had bilirubin level between >15 to 19 mg/dl and 7 (11.11%) had bilirubin levels more than 19 mg/dl. (Table 2)

ABO incompatibility was observed in 68 (26.36%) babies, out of which 37 (54.41%) were male and 31 (45.59%) were female. RH incompatibility was observed in 20 (7.75%) babies with 12 (60%) male and 8 (40%) female.

In 50 (19.38%) babies the cause of hyperbilirubinemia was not known. Out of these 50 babies 26 (52%) were male and 24 (48%) were female.

Out of 63 premature babies, 46 (17.83%) other causes of hyperbilirubinemia were ruled out and prematurity itself was assigned as a cause of hyperbilirubinemia. Out of these 46 babies 27 (58.75) were male and 19 (41.3%) were female.

Sepsis was the cause of hyperbilirubinemia in 26 (10.08%) babies among them 15 (57.7%) were male and 11(42.3%) with female.

G6PD deficiency was observed in 18 (6.98%) babies among them 10 (55.6%) were male and 8 (44.4%) were female.

There were 11 (4.26%) infant of diabetic mother who had hyperbilirubinemia out of which 6 (54.5%) were male and 5 (45.5%) were female.

Breast milk jaundice was seen in 8 (3.10%) babies out of which 5 (62.5%) were male and 3 (37.5%) were female.

Hyperbilirubinemia with cephalhematoma was observed in 4 (1.55%) babies with equal male 2 (50%) and female 2 (50%) distribution.

Hypothyroidism was the cause of neonatal hyperbilirubinemia in 3 cases with identical number seen in polycythemia as well. Gender distribution in case of hypothyroidism was 1(33.3%) male baby and 2(66.7%) female babies whereas it was just the opposite in case of polycythemia where 2 (66.7%) babies were male and 1 (33.3%) was female.

One (0.39%) baby with Down's syndrome also had hyperbilirubinemia. (Table 3)

Features of bilirubin encephalopathy (kernicterus) was seen in 2 neonates and both the babies had G6PD deficiency too.

Amongst the 258 neonates all the babies had received phototherapy as a part of the treatment for hyperbilirubinemia whereas only 21 babies had to undergo exchange transfusion.
Table 1. Gender distribution in neonates with hyperbilirubinemia

| Gender | No of Neonates N = 258 (%) |
|--------|-----------------------------|
| Male   | 144 (55.8)                  |
| Female | 114 (44.2)                  |

Figure 1. Pie chart showing gender distribution in neonates with hyperbilirubinemia

Table 2. Serum bilirubin levels in Term and Preterm Neonates

| Serum Bilirubin | Full Term Neonates | Pre Term Neonates |
|-----------------|--------------------|-------------------|
| < 17 mg/dl      | 195 (75.58%)       | 63 (24.42%)       |
| > 17 – 20 mg/dl | 67                 | 25                |
| > 20 mg/dl      | 19                 | 7                 |

Table 3. Causes of Neonatal Hyperbilirubinemia

| Various Causes          | Male babies No with Percentage | Female babies No with Percentage |
|-------------------------|--------------------------------|---------------------------------|
| ABO incompatibility     | 37 (54.11%)                   | 31 (45.59%)                     |
| Rh incompatibility      | 12 (60%)                      | 8 (40%)                         |
| Rh incompatibility      | 10 (55.6%)                    | 8 (44.4%)                       |
| Sepsis                  | 15 (57.7%)                    | 11 (42.3%)                      |
| G6PD Deficiency         | 6 (55.6%)                     | 5 (45.5%)                       |
| Infant of DM mother     | 5 (54.5%)                     | 5 (45.5%)                       |
| Breast Milk Jaundice    | 5 (62.5%)                     | 3 (37.5%)                       |
| Cephalhematoma          | 2 (50%)                       | 2 (50%)                         |
| Hypothyroidism          | 1 (33.3%)                     | 2 (66.6%)                       |
| Polycythemia            | 2 (66.6%)                     | 1 (33.3%)                       |
| Down’s syndrom          | 1 (100%)                      | 0 (0%)                          |
DISCUSSION

Hyperbilirubinemia is quite common in newborns and multiple factors are responsible for its occurrence. A review article published in North America suggested that the etiology of neonatal hyperbilirubinemia is multifactorial (3), and we also obtained similar results. In our study, out of 258 babies, 144 were male and 114 were female. Male preponderance was observed in previous publications too (4,5).

ABO incompatibility was the most common cause of pathological hyperbilirubinemia in our study, with 26.36% of babies having ABO incompatibility similar to the results of other studies. Study done by Anil Shetty et al: Neonatal hyperbilirubinemia in a tertiary care hospital showed ABO incompatibility as the most common cause of hyperbilirubinemia (6, 7). Similar study done by Mishra et al: Hematological profile in neonatal jaundice showed 20% of neonates develop hyperbilirubinemia due to ABO incompatibility (4,8).

Idiopathic as an etiology was observed in 15.5% cases in a study by Singh S K et al (9). In our study, in 19.38% cases, a definite cause could not be ascertained. Similar findings were observed in an Iranian study where 118 neonates were investigated for the cause of neonatal hyperbilirubinemia and the researchers revealed that in 25.4% of neonates the etiology could not be ascertained (10). A Canadian study also revealed that in the majority of neonatal hyperbilirubinemia cases, the underlying cause was not identified (11). Many authors have not been able to establish the etiology of hyperbilirubinemia in more than half of the cases in their series (12).

Prematurity is an important cause of neonatal hyperbilirubinemia and has been well documented in the literature (13-15). In our study, too, as many as 18% of the cases were due to prematurity.
Sepsis is a significant cause of neonatal hyperbiliru-
binemia and the fact is supported by a very large
number of literature published worldwide (16, 17).
Another important cause of hyperbilirubinemia is Rh incompatibility. Rh incompatibility has been
shown as a risk factor for hyperbilirubinemia in newborns in many studies (4,9,18,19).
G6PD deficiency is a fairly common cause of neonatal hyperbilirubinemia but not investigated
routinely in developing countries particularly because of the cost involved, as also observed in a
study by Anil Shetty et al (5). G6PD deficiency can lead to severe neonatal hyperbilirubinemia, as
reported in many studies. In a study conducted by Basoi S et al in a tertiary care hospital in West
Bengal showed that 14.68% of the newborn were G6PD deficient and 23.8% of them developed
severe neonatal hyperbilirubinemia compared to 12.5% of non G6PD deficient who developed severe
neonatal hyperbilirubinemia (20). A cohort study was carried out to access the association between G6PD
deficiency and neonatal hyperbilirubinemia. Data suggest that the G6PD deficient neonates are at
increased risk of hyperbilirubinemia even in the nursery free from agent that can potentially cause
hemolysis to G6PD deficient red cells. (21) Although hemolysis may be observed in neonates who have
G6PD deficient and are jaundiced. (22) Other mechanisms appear to play a more important role in
the development of hyperbilirubinemia. (23, 24, 25)
Infant born to diabetic mothers are also prone to
hyperbilirubinemia. In our study too we had 11
neonates born to diabetic mother who had
hyperbilirubinemia. Studies shows that large for
gestational age infant of diabetic mother are at
increased risk of hyperbilirubinemia then average
for gestational age infant of diabetic mother and infant of non diabetic mothers and that increased
heme turnover is a significant factor in the pathogenesis (26).
Breast milk jaundice occurs later in the newborn
period with the bilirubin level usually peaking in the
6th to 14th day of life (27). This late onset jaundice
can develop in up to one third of healthy breast fed
infants (28). The underlying cause of breast milk
jaundice is not clearly understood. Substance in
maternal milk suggests beta glucuronidases and non
esterified fatty acids, may inhibit normal bilirubin metabolism (29-32).
Cephalhematoma is a rare but not uncommon cause
of hyperbilirubinemia. In our study we had 4 babies
with Cephalhematoma leading to hyperbilirubin-
emia. Hypothyroidism polycythemia and Down's
syndrome can also lead to hyperbilirubinemia in
many neonates and this is well documented in many
studies. In our study too few cases were seem to
develop hyperbilirubinemia due to the above three
causes.

CONCLUSION
ABO incompatibility is very common cause of neonatal hyperbilirubinemia. Although historically
Rh incompatibility has been accorded much importance, ABO incompatibility should alert the
attending doctor about the impending risk of significant neonatal jaundice. If discharged early
written protocol should be followed where a revisit
should be planned within 1 to 3 days for babies with
any risk factors so that hyperbilirubinemia if any is
detected and treated accordingly to prevent long
term neurological morbidity. In this era where India
has achieved significant advancement in the field of
Medical Science, even a few cases of bilirubin
encephalopathy and its associated sequelae is a grim
reminder of the state of affairs of our health delivery
system and ignorance among the population at
large. Much needs to be done to spread awareness
particularly in the rural areas where people still
approach traditional healers to treat jaundice leading
to delay in timely medical interventions.

BIBLIOGRAPHY
1. Ambalavanan N, Carlo W A. Jaundice and
Hyperbilirubinemia in the Newborn. 1st
South Asia Eds. Kliegman R M, Stanton B
F, Gene J W, Schor N F. Nelson Textbook
of Pediatrics. Vil 1. Elsevier; 2016: 871.
2. Gregory M L P, Martin C R, Cloherty J P.
Neonatal Hyperbilirubinemia. 7th Eds.
Cloherty J P, Eichenwald E C, Hansen A R,
Stark A R. Manual of Neonatal Care.
Lippincott Williams and Wilkins; 2012: 307.
3. Watchoko JF. Identification of neonates at risk for hazardous hyperbilirubinemia: Emerging clinical insights. Pediatr clin North Am 2009; 56 (3): 671-87.

4. Mishra et al: Hematological profile in neonatal jaundice. J Basic Clin Physiol Pharmacol 2014 May 1; 25 (2): 225-8.

5. Najib K, Saki F, Hemmati F, Inaloo S. Incidence risk factor and causes of severe neonatal hyperbilirubinemia in South of Iran. (Fars Provinces). Iran Red Cross Med J 2013; 15: 260-3.

6. Shetty A, Kumar B S. A study of neonatal hyperbilirubinemia in a tertiary Care Hospital. Int J Med Sci Public Health 2014; 3: 1289-1292.

7. Davutoglu M, Garipardic M, Guler E, Karabiber H, Erhan D. The etiology of severe neonatal hyperbilirubinemia and complications of exchange transfusion. Turk J Pediatr 2010; 52 (2): 163-6.

8. Badiee Z. Exchange transfusion in neonatal hyperbilirubinemia: Experience in Isfahan, Iran. Singapore Med J 2007; 48: 421-3.

9. Singh S K, Singh S N, Kumar M, Tripathi S, Bhriguavansi A, Chandra T, Kumar A. Etiology and clinical profile of neonates with pathological unconjugated hyperbilirubinemia with special reference to Rhesus (Rh) D, C, and E incompatibility: A tertiary care centre experience. Clinical Epidemiology and global Health 4. 2016; 95 – 100.

10. Heydarian F, Majdi M. Hydarian F, Majdi M. Severe neonatal hyperbilirubinemia; Causes and contributing factors leading to exchange transfusion at Ghaem Hospital in Mashhad. Acta Med Iran 2010; 48 (6): 399-402.

11. Sgro M, Campbell D, Shah V. Incidence and causes of severe neonatal hyperbilirubinemia in Canada. CMAJ 2006; 175 (6): 587 – 90.

12. Narang A, Gath Wala G, Kumar P. Neonatal jaundice: An analysis of 551 cases. Indian pediatr. 1997; 34: 429-432.

13. Ho N K. Neonatal jaundice in Asia. Baillieres. Clin Haematol 2002; 5: 131 - 142.

14. Mishra S, Agarwal R, Deorari A K. Jaundice in the newborns. Indian J pediatr 2008; 75: 157-63.

15. Sarici S U, Serdar M A, Karkmaz A, Erdem G, Oran O, Tekinalp G et al. Incidence, course and prediction of hyperbilirubinemia in near term and term newborns. Pediatrics 2014; 113 (4): 775-80.

16. Kaplan M, Wong R J, Sibley E, Stevenson D K. Neonatal jaundice and liver disease. 9th ed. Martine R J, Fanaroff A A, Walsh M C, eds Neonatal – Perinatal Medicine: Diseases of Fetus and Infant. Vol 2. St Louis: Elsevier Mosby; 2011: 1443.

17. Maisels M J, Kring E. Risk of sepsis in newborn severe hyperbilirubinemia. Pediatrics. 1992; 90: 741-743.

18. Dennery P A, Seidman D S, Stevenson D K. Neonatal hyperbilirubinemia. N Engl J Med. 2001; 344: 581-90.

19. Clemons RM. Issues in newborn care. Prim Care. 2000; 27: 251-67

20. Biso S, Chakraborty S, Chatopadhyay D, Biswas B, Ray S. glucose 6 phosphate dehydrogenase screening of babies born in a tertiary care hospital in West Bengal. Indian J Public Health 2012; 56 (2): 146-8.

21. Weng Y H, Chou Y H, Lien R I. Hyperbilirubinemia in healthy neonates with G6PD deficiency. 2003 Apr; 71 (2): 129-36.

22. Bizzarro M J, Colson E, Ehrenkranz RA. Differential Diagnosis and management of anemia in the newborn. Pediatric Clin North Am. 2004; 51: 1087-107.

23. Butler E. G6PD deficiency. Blood. 1994; 84: 3613-36.

24. Kaplan M, Vreman H J, Hammerman C, Abramov A, Stevenson D K. Contribution of hemolysis to jaundice in Sephardic Jewish glucose 6 phosphate dehydrogenase deficient neonates. Br J Haematol.1996;93:822 - 7

25. Seidman D S, Shiloh M, Stevenson D K, Verman H J, Gale R. Role of Himalayas in
neonatal jaundice associated with glucose 6 phosphate dehydrogenase deficiency. J Pediatr. 1995; 127: 804 - 6.

26. Peevy K J, Landaw S A, Gross S J. Hyperbilirubinemia in infants of diabetic mothers. Pediatrics. 1980 Sep; 66 (3):417 - 9

27. Meredith L. Peter, Cpt MC USA. Beth L Dennis, Maj MC USA. Hyperbilirubinemia in term newborn. Am Fam Physician. 2002 Feb; 65 (4): 599 - 607.

28. Practice parameter: Management of hyperbilirubinemia in the healthy term newborn. Paediatrics. 1994;944 pt 1:558-62.

29. Melton K, Akinbi H T. Neonatal jaundice. Strategies to reduce bilirubin induced complications. Postgrad Med. 1999; 106: 167-8, 171-4, 177-8.

30. Gartner L M, Herschel M. Jaundice and breast-feeding. Pediatr Clin North Am. 2001; 48: 389-99.

31. Poland R L. Breast milk jaundice. J Pediatr. 1981; 99: 86-8.

32. Brodersen R, Herman L S. Intestinal reabsorption of unconjugated bilirubin. Lancet. 1963; 1: 1242.