Review Article

Pediatric Education and Research
Volume 7 Number 2, April - June 2019
DOI: https://dx.doi.org/10.21088/per.2321.1644.7219.4

Risk factors of Neonatal Hyperbilirubinemia

Amar Taksande[1], Sinduja[2]

[1]Professor, [2]Resident, Department of Pediatrics, Jawaharlal Nehru Medical College, Sawangi Meghe, Wardha, Maharashtra 442004, India.

How to cite this article:
Amar Taksande, Sinduja. Risk factors of Neonatal Hyperbilirubinemia. Pediatr Edu Res. 2019;7(2):59-64.

Abstract

Jaundice is the yellowish discoloration of the sclera and the skin due to increased bilirubin levels in blood. It is often a normal condition in the neonates, but when the levels of the bilirubin exceed a certain range, it requires intervention because it can have serious neurological sequelae and may even cause death in those who survive. There are some factors which can put the baby at an increased risk of developing hyperbilirubinemia. These risk factors may be maternal or neonatal. Maternal risk factors can include any history of drugs, other comorbid conditions, ABO and Rh incompatibility, ethnicity and others. Neonatal risk factors include gestational age, infections, trauma during birth, etc.

Keywords: Jaundice; Neonatal Hyperbilirubinemia; Bilirubin levels.

Introduction

Jaundice is the most common condition in neonates that requires medical attention and hospital readmission [1]. It is the yellowish discoloration of the sclera and the skin due to increased bilirubin levels in blood. It is often a normal condition in the neonates, but when the levels of the bilirubin exceed a certain range, it requires intervention because it can have serious neurological sequelae and may even cause death in those who survive. Therefore earlier recognition and appropriate intervention is required. It is classified as physiological when it appears in the first week of life, from day 2 to day 7 of life. About 60% of term infants develop jaundice in the first week. The incidence is much higher in preterm infants, about 85%. The jaundice is said to be pathological when it appears in the first 24 hours after birth or after the first week.

Hyperbilirubinemia can be due to increased levels of unconjugated bilirubin or due to increased levels of conjugated bilirubin levels. In neonates, most often, hyperbilirubinemia is due to increased levels of unconjugated bilirubin levels. In neonates, dermal icterus is first noticed in the face and proceeds downwards towards the rest of the body

Corresponding Author: Amar Taksande, Department of Pediatrics, Jawaharlal Nehru Medical College, Sawangi Meghe, Wardha, Maharashtra, 442004, India.

E-mail: amar.taksande@gmail.com

Received on 28.03.2019, **Accepted on** 20.05.2019

as the bilirubin levels increase [2-3]. There are some factors which can put the baby at an increased risk of developing hyperbilirubinemia. These risk factors may be maternal or neonatal. Maternal risk factors can include any history of drugs, other comorbid conditions, ABO and Rh incompatibility, ethnicity and others. Neonatal risk factors include gestational age, infections, trauma during birth, etc.

Maternal Risk factors for hyperbilirubinemia

a. ABO incompatibility

This is a type of immunogenic jaundice in which, the mother's antibodies are transferred to the fetus causing breakdown of the fetal RBC's, leading to hyperbilirubinemia. This occurs when the mother has blood group O. The antibodies in the blood of the mother may be transferred across the placenta and can cause lysis of the fetal RBC's This is less severe than Rh incompatibility because the ABO blood group antigens are expressed in many other tissues and this reduces the chances of the antibodies binding to the RBC's of the fetus. Also the fetus expresses fewer levels of the ABO group antigens [4-5].

b. Rh incompatibility

It is a major cause of hemolytic disease of the newborn. The risk is many times more when the mother is Rh D-negative caring an Rh D-positive child. Although other forms of Rh factor like c, C, e, E can also cause haemolysis, the incidence is less common. The direct Coombs test is used to identify those fetal RBC which are already bound by the anti D antibody, whereas the indirect Coombs test is used to detect the levels of anti-D antibody in the maternal serum [6]. This can be prevented from early recognition and administration of the anti D Ig and serial monitoring of the fetus until the Rh status of the fetus can be confirmed [5-6].

c. Drugs taken by the mother

Oxytocin, bupivacaine, antenatal dexamethasone have been associated with increased risk of jaundice. 10 -13% of neonatal hyperbilirubinemia may be due to oxytocin use. These drugs can cross placenta and enter the fetal circulation. Some of these drugs can cause the bilirubin to be displaced from the albumin and increase the levels of bilirubin in the blood [7-8].

d. Ethnicity

A study conducted by Setia S et al. [9], showed that babies born to asian parents were found to have higher risk of developing jaundice when compared to their white, age and risk factors matched individuals. Asian babies were all found to have recognized gene mutations relating to hyperbilirubinemia.

e. Previous sibling with hyperbilirubinemia

A study by Khoury MJ et al. [10] mentioned that the increased risk of hyperbilirubinemia in infants with a sibling treated for the same, has a familial factor and no role of environmental factors.

f. Mode of delivery

Babies born by oxytocin induced vaginal delivery have higher bilirubin levels than those born by LSCS. Vacuum extraction is also associated with increased incidence of jaundice [7-8].

g. Maternal age

A study conducted by Srivastav et al. [11] showed that the incidence of neonatal hyperbilirubinemia was greater in younger mothers. Another study by Zhang B et al. [12] showed that the relative incidence of neonatal hyperbilirubinemia is associated with maternal age, with a peak in incidence at 26 years of age.

h. Infants of diabetic mother (IDM)

Macrosomia, commonly found in IDM, can cause increased risks of trauma during delivery and have higher rates of induced labor and Caesarean sections, these babies are also more prone to have polycythemia. These factors, by themselves, also contribute to the increased bilirubin levels. A study conducted by Peevy KJ et al. [13] showed that Large for gestational age babies born to diabetic mother were associated with higher levels of Hyperbilirubinemia when compared to appropriate for age (AGA) infants of diabetic mother and infants born to normal mothers. This was attributed by the study to an increased heme -turnover, measured by carboxyhemoglobin levels.

i. Breast feeding jaundice

Breast feeding jaundice is a preventable form of jaundice, which occurs due to caloric deficiency and or due to insufficient feeding of the neonate. It may be because the baby does not get adequate milk, does not have a good latch or is not fed frequently enough. It can also be because the breast milk has been replaced by some other substitute

or if the mother has an improper diet leading to decreased secretion. When the baby is not well fed the baby may go into dehydration and there is decreased excretion of unconjugated bilirubin from the blood, an increased eneterohepatic re-uptake of bilirubin leading to hyperbilirubinemia. Breast milk increases the movements of the bowel, helping to secrete the accumulating bilirubin, thus decreasing the incidence of jaundice. A weight loss of about 7-10%, by day 3 is an indication of inadequate breast feeding. Therefore daily weight monitoring and adequate and proper breastfeeding can reduce the incidence of breastfeeding Jaundice [5-9].

Perinatal Risk Factors for hyperbilirubinemia

a. Infections

Sepsis results in jaundice, early in the first week of life but is also accompanied by other signs of sepsis. The most common cause is Group B streptococcous, followed by E.coli and then other organisms. The underlying mechanism has been attributed to several factors including cholestasis, acidosis and increased hemolysis of RBCs. Urinary tract infections is the one of the causes of infection associated with neonatal jaundice. It presents with jaundice after the first week of life, is moderate, resembles physiological jaundice and may not require any treatment. The causative organisms can be Klebsiella, E. coli, Staphylococcus epidermidis, Staphylococcus aureus and Acineobacter. The hyperbilirubinemia is probably due to hemolysis caused by gram negative organisms [13-15].

b. Birth Trauma

Blood sequestration like haematoma, those caused due to bruising during delivery and intracranial haemorrhage can cause increase in the load of bilirubin levels in the neonate, taxing the immature liver conjugation enzymes, leading to hyperbilirubinemia.

i. Hematoma: This usually refers to extra cranial injuries that result in oedema or bleed in different regions of the scalp or skull and other regions as a result of injury received during delivery. They made be cephalohematoma, subgaelel hematoma, bruising during delivery. These injuries could be due to instrumental delivery, Cephalo-pelvic disproportion, large for gestational age (LGA) babies and breech deliveries.

ii. Intracranial haemorrhage: Subdural (SDH) and intra-parenchymal haemorrhage are more common in term infants whereas primary Subarachnoidal (SAH), intra ventricular haemorrhage (IVH) and cerebral haemorrhage are more common in preterrm infants. The risk of intracranial haemorrhage increases in neonates born from protracted or precipitous labor, instrumental delivery such as forceps, ventouse extraction, vaginal breech delivery, in primiparity [15-18].

Neonatal Risk factors for hyperbilirubinemia

a. Birth weight and gestational age

Low birth weight babies and small for gestational age babies are at high risk neonatal hyperbilirubinemia. 36-38 weeks babies are at 7-8 times high risk; babies <36 weeks are 13 times more risk for hyperbilirubinemia [16-19].

b. Gender

Male gender is a known risk factor for hyperbilirubinemia. Higher incidence of hyperbilirubinemia was found in male babies as compared to female babies which was reported by Tioseco JA et al. (17).

c. Glucose-6-phosphate dehydrogenase (G6PD) deficiency

It is an X-linked recessive disorder. The G6PD is required for the production of Nicotinamide adenine dinucleotide phosphate (NADPH) in the body. It is found in abundance in RBC and helps to combat oxidative stress. It is the only source of NADPH in the RBC's, where oxidative stress in maximum, due to their role as oxygen carriers. Therefore deficiency of this enzyme less to hemolysis of RBC's which increase during periods of oxidative stress. Neonatal jaundice is one of the earliest presentation of this disease, with a peak in jaundice during the second or the third day of life [20].

d. Pyruvate kinase deficiency

It is an autosomal recessively inherited enzyme defect. The enzyme is a part of the glycolytic pathway. This enzyme plays an important role in RBC as they produce Adenosine Triphosphate (ATP) only through anaerobic glycolysis. The deficiency of this enzymes thus leads to increased breakdown of RBC and increases the risk of hyperbilirubinemia in neonates. Few studies have been done to analyse the prevalence of pyruvate kinase deficiency in India. Kedar et al. [21] reported that the prevalence of PK deficiency in Indian neonatal jaundice cases is 3.21%, which is relatively high. All of the neonates with this deficiency presented with unconjugated

hyperbilirubinemia and reticulocytosis in the first 2 weeks.

e. Hereditary spherocytosis

It is inherited in an autosomal dominant or recessive pattern, with severity being more in the recessive pattern. In neonates with hyperbilirubinemia, an mean corpuscular hemoglobin concentration (MCHC) of 32 or greater, Mean corpuscular volume (MCV) is usually in normal range, and spherocytes on peripheral smear, should arouse a suspicion of hereditary spherocytosis. A direct Coombs test (DCT) can rule out auto-immune hemolytic anaemia and ABO incompatibility as a cause of spherocytosis. Osmotic fragility test can be done in neonates, but the RBC in neonatal period are more resistant to hemolysis, so neonatal control should be used. The definitive treatment is splenectomy [22-23].

f. Elliptocytosis

It is usually diagnosed based on the presence of oval or elliptical RBC on peripheral smear. It is usually goes undetected as it is either asymptomatic or causes moderate hyperbilirubinemia in the neonatal period, unless it is inherited with other disorders of RBC [24].

g. Conditions which decreased hepatic uptake and conjugation

i. Gilbert syndrome

It is a benign condition of the liver, in which the liver cannot properly conjugate the bilirubin due to an insufficiency of a liver enzyme known as uridine disphosphate-glucuronosyl transferase-1A1 (UGT1A1) that is coded by UGT1A1 gene, due to promoter defects that results in mis-sense mutations. This disease is usually diagnosed in adolescent, due to yellowish discoloration of the eyes and skin. It is inherited as an autosomal recessive pattern. A study conducted by Forough Sakai et al showed that the Gilbert syndrome does not in itself cause severe hyperbilirubinemia but associated with other risk factors may contribute to increased levels of bilirubin [25-26].

ii. Crigler Najjar syndrome

This is of two types, both of which are inherited in an autosomal recessive pattern. Type 1 is more predominant in infancy and can result in increased levels of bilirubin during neonatal period. It is associated with the complete deficiency of UGT1A1 activity. This reduces the UDP glucoronyl transferase activity and increases the levels of unconjugated bilirubin levels in blood. Early liver transplantation is the best treatment to prevent death and ongoing brain damage [27]. CN type 11, has reduced activity of enzymes UDP glucosenyltransferase. It may present in infancy or in adults.

iii. Pyloric stenosis

The exact mechanism of hyperbilirubinemia in hypertrophic pyloric stenosis is not known but it has been attributed to decrease in activity of hepatic glucoronyl transferase or increased activity of intestinal glucuronidase, which converts the conjugated bilirubin to the unconjugated form and increases the reuptake of bilirubin through the enterohepatic system [28].

iv. Hypothyroidism

Congenital hypothyroidism is well known cause of prolonged neonatal jaundice. The exact cause of hyperbilirubinemia in congenital hypothyroidism is not known but it has been implicated with the delayed maturation of the liver enzymes, like uridine glucoronyl transferase, cholestasis and decreased metabolism of bilirubin. It is one the causes of preventable intellectual disability [29].

h. Conditioned which increased enterohepatic reabsorption

i. Bowel obstruction

Bowel obstruction in the neonates like duodenal atresia, jejunal atresia, malrotation, iliac atresia, meconium plug, can cause biliary cholestasis and increased hepatic reuptake of bilirubin by the enterohepatic circulation. This is a type of pathological jaundice that requires surgical repair.

The conjugated form of bilirubin is converted to unconjugated forms which can be taken up into the enterohepatic circulation. The jaundice usually evolves after the defect is repaired [30].

ii. No enteric feeding

It has been found that fasting increases the levels of enterohepatic circulation by decreasing gut motility in infants. Total parental nutrition in the neonates can be a cause of cholestasis, due to decreased motility in neonates, resulting in

neonatal hyperbilirubinemia. A positive correlation has been found with the early initiation of feeding that is feeding within the first hour of life and the levels of bilirubin in blood after 24 hours [31-32].

iii. Delayed meconium passing

The delayed passage or decreased frequency of meconium makes bilirubin in meconium available for enterohepatic circulation and may increase the possibility of hyperbilirubinemia [33]. Although studies conducted to evaluate the effect of early passage of mecum on serum bilirubin levels were inconclusive.

Other factors

a. Early discharge from the hospital

Discharge from the hospital at or before 48 hours postpartum increases risk of hyperbilirubinemia development because neonates are home, not under direct medical supervision at age 3 to 5 days when bilirubin levels are most likely to peak [34-35].

b. Influence of season on bilirubin levels

In a study conducted by Bala J et al. [36], it was found that the risk of neonatal hyperbilirubinemia is more in infants born in the summer than those born in the winter. This can be associated with an increase in the ambient temperature and an increased frequency of breast feeding which can inhibit the liver enzymes and reducing the conjugation of the bilirubin in the blood.

Conclusion

Hyperbilirubinemia is one of the most common causes of hospital readmission in the neonatal age group. It has been associated with various risk factors. Severe hyperbilirubinemia can result in significant neuro-developmental damage. Early recognition of infants at risk, proper examination and follow up with timely intervention, can reduce the morbidity and mortality of hyperbilirubinemia.

References

1. Olusanya BO, Osibanjo FB, Slusher TM. Risk factors for severe neonatal hyperbilirubinemia in low and middle-income countries: a systematic review and meta-analysis. PLoS One. 2015 Feb 12;10(2):e0117229.
2. Stoll BJ, Kliegman RM. Jaundice and hyperbilirubinemia in the Newborn. In: Behrman RE, Kliegman RM, Jenson HB, Eds. Nelson Textbook of Pediatrics. 19th ed. Philadelphia: WB Saunders Co. 2012.pp.603-605.
3. Practice parameter: management of hyperbilirubinemia in the healthy term newborn. American Academy of Pediatrics. Provisional Committee for Quality Improvement and Subcommittee on Hyperbilirubinemia. Pediatrics. 1994 Oct;94(4 Pt 1):558-65.
4. Knudsen A. Prediction and non-invasive assessment of neonatal jaundice in the term healthy newborn infant. Acta Paediatr. 1996;85:393-7.
5. Pathak U, Chawla D, Kaur S, Jain S. Bilirubin nomogram for prediction of significant hyperbilirubinemia in north Indian neonates. Indian Pediatr. 2013;50(4):383-9.
6. Dillon A, Chaudhari T, Crispin P, Shadbolt B, Kent A. Has anti-D prophylaxis increased the rate of positive direct antiglobulin test results and can the direct antiglobulin test predict need for phototherapy in Rh/ABO incompatibility? J Paediatr Child Health. 2011 Jan;47(1-2):40-3.
7. Cherepnalkovski AP, Krzelj V, Zafirovska-Ivanovska B, Gruev T, Markic J, Aluloska N et al. Evaluation of Neonatal Hemolytic Jaundice: Clinical and Laboratory Parameters. Open Access Maced J Med Sci. 2015 Dec 15;3(4):694-8.
8. Singla DA, Sharma S, Sharma M, Chaudhary S. Evaluation of Risk Factors for Exchange Range Hyperbilirubinemia and Neurotoxicity in Neonates from Hilly Terrain of India. Int J Appl Basic Med Res. 2017 Oct-Dec;7(4):228-232.
9. Najib K, Saki F, Hemmati F, Inaloo S. Incidence, risk factors and causes of severe neonatal hyperbilirubinemia in South of Iran (Fars Province). Iran Red Cres Med J. 2013;15(3):260-3. DOI: 10.5812/ircmj.3337.
10. Setia S, Villaveces A, Dhillon P, Mueller BA.Neonatal jaundice in Asian, white, and mixed-race infants. Arch Pediatr Adolesc Med. 2002 Mar;156(3):276-9.
11. Khoury MJ, Calle EE, Joesoef RM. Recurrence risk of neonatal hyperbilirubinemia in siblings.Am J Dis Child. 1988 Oct;142(10):1065-9.
12. Zhang B, Zhu H, Chen P and Ding Q. The Association of Neonatal Jaundice with the Age of Parents. Austin Biol. 2016;1(3):1013.
13. Srivastav N, Pande US, Malik GK, Singh SS, Singh SK. A study of serum bilirubin in neonates in relation to the maternal age. Indian J Med Sci. 1999 Apr;53(4):158-61.
14. Peevy KJ, Landaw SA, Gross SJ. Hyperbilirubinemia in infants of diabetic mothers. Pediatrics. 1980 Sep;66(3):417-9.
15. Shahian M, Rashtian P, Kalani M. Unexplained

neonatal jaundice as an early diagnostic sign of urinary tract infection. Int J Infect Dis. 2012 Jul;16(7):e487-90.

16. Wong F, Boo N, Othman A.Risk factors associated with unconjugated neonatal hyperbilirubinemia in Malaysian neonates. J Trop Pediatr. 2013 Aug;59(4):280-5.
17. Joshi BD, Singh R, Mahato D, Prasad R. Clinico-laboratory profile of neonatal hyper-bilirubinemia in term babies at B.P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal. J Nepal Health Res Counc. 2004 Oct;2:28–30.
18. Tioseco JA, Aly H, Milner J, Patel K, El-Mohandes AA. Does gender affect neonatal hyperbilirubinemia in low-birth-weight infants? Pediatr Crit Care Med. 2005 Mar;6(2):171–74.
19. Chawla D, Jain S, Dhir S, Rani S. Risk assessment strategy for prediction of pathological hyperbilirubinemia in neonates. Indian Pediatr. 2011;79(2):198–201.
20. Morioka I. Hyperbilirubinemia in preterm infants in Japan: New treatment criteria. Pediatr Int. 2018 Aug;60(8):684-690.
21. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet. 2008 Jan 5;371(9606):64–74.
22. Kedar PS, Warang P, Colah RB, Mohanty D.Red cell pyruvate kinase deficiency in neonatal jaundice cases in India. Indian J Pediatr. 2006 Nov;73(11):985-8.
23. Agarwal MB, Kumud PM, Mehta BC. Hereditary spherocytosis in a neonate. Indian Pediatr. 1979;16: 359-61.
24. Huang MJ, Kua KE, Teng HC, Tang KS, Weng HW, Huang CS. Risk factors for severe hyperbilirubinemia in neonates. Pediatr Res. 2004 Nov;56(5):682–89.
25. Christensen RD, Nussenzveig RH, Reading NS, Agarwal AM, Prchal JT, Yaish HM. Variations in both α-spectrin (SPTA1) and β-spectrin (SPTB) in a neonate with prolonged jaundice in a family where nine individuals had hereditary elliptocytosis. Neonatology. 2014;105(1):1-4.
26. Kaur S, Chawla D, Pathak U, Jain S. Predischarge non-invasive risk assessment for prediction of significant hyperbilirubinemia in term and late preterm neonates. J Perinatology. 2012;32:716–21.
27. Slachtova L, Seda O, Behunova J, Mistrik M, Martasek P.Genetic and biochemical study of dual hereditary jaundice: Dubin-Johnson and Gilbert's syndromes. Haplotyping and founder effect of deletion in ABCC2. Eur J Hum Genet. 2016 May;24(5):704-9.
28. Liaqat A, Shahid A, Attiq H, Ameer A, Imran M. Crigler-Najjar Syndrome Type II Diagnosed in a Patient with Jaundice Since Birth. J Coll Physicians Surg Pak. 2018 Oct;28(10):806-08.
29. Akzhigitov GN, Shapiro EE. Congenital hypertrophic pyloric stenosis associated with hyperbilirubinemia. Pediatriia. 1990;(11):100-1.
30. Tiker F, Gurakan B, Tarcan A, Kinik S. Congenital hypothyroidism and early severe hyperbilirubinemia. Clin Pediatr (Phila). 2003 May;42(4):365-6.
31. Hara K, Kinoshita M, Kin T, Arimitsu T, Matsuzaki Y, Ikeda K et al. A neonate with intestinal volvulus without malrotation exhibiting early jaundice with a suspected fetal onset. Turk J Pediatr. 2015 Jul-Aug;57(4):418-421.
32. Barseghyan K, Ramanathan R, Chavez T, Harlan S, Lin CH, Mitsinikos T et al. Utility of hepatobiliary scintigraphy in diagnosing or excluding biliary atresia in premature neonates and full-term infants with conjugated hyperbilirubinemia who received parenteral nutrition. Matern Fetal Neonatal Med. 2018 Dec;31(24):3249-54.
33. Nielsen HE, Haase P, Blaabjerg J, Stryhn H, Hilden J. Risk factors and sib correlation in physiological neonatal jaundice. Acta Paediatr Scand. 1987 May;76(3):504–11.
34. Bader D, Yanir Y, Kugelman A, Wilhelm-Kafil M, Riskin A. Induction of early meconium evacuation: is it effective in reducing the level of neonatal hyperbilirubinemia?. Am J Perinatol. 2005 Aug;22(6):329-33.
35. Geiger AM, Petitti DB, Yao JF. Rehospitalisation for neonatal jaundice: risk factors and outcomes. Paediatr Perinat Epidemiol. 2001 Oct;15(4):352–358.
36. Michael S, Douglas C, Vibhuti S. Incidence and causes of severe neonatal hyperbilirubinemia in Canada. 2006;6:175.
37. Bala J, Agrawal Y, Chugh K, Kumari M, Goyal V, Kumar P. Variation in the serum bilirubin levels in newborns according to gender and seasonal changes. Arch Med Health Sci. 2015;3:50-5.