A study of predictors & prevalence of neurodevelopmental outcome in hyper-bilirubinemic neonates admitted in NICU

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Abstract

Background: Hyper-bilirubinemia may be toxic to the developing central nervous system and may cause neurological impairment. This study was conducted to identify factors of abnormal neurodevelopment at 3 & 12 months in babies having birth weight >1.5 kg and gestational age >34 weeks with neonatal hyper-bilirubinemia.

Methods: This prospective study was conducted at Sardar Patel Medical College, Bikaner (Rajasthan) from 2014 to 2015. Hyper-bilirubinemic newborns were examined at 3 and 12 month age and their neurodevelopmental assessment was done by DASII method. All the collected data was tabulated and statically analyzed by using SPSS software.

Results: 69.79% of hyper-bilirubinemic neonates were males & 30.21% were females. The prevalence of neurodevelopmental abnormalities (DQ≤70) was 10.42% at 3 months where as it was 6.25% at 12 months follow up suggesting reversibility of adverse neurodevelopment. Early onset of jaundice (≤1 day), serum bilirubin level >25 mg/dl, duration of hospital stay>3 days and requirement of exchange transfusion was significantly associated with adverse neurodevelopmental outcomes (DQ≤70) at 3 and 12 months of age on follow up.

Conclusion: This Prospective observational study found a high prevalence of adverse neurodevelopmental outcome in neonates with hyper-bilirubinemia with risk factors. Early detection of neurodevelopmental abnormalities and initiation of early intervention measures to reduce the prevalence of neurodevelopmental abnormalities in hyper-bilirubinemic neonates.

Keywords: Hyper-bilirubinemia, Neurodevelopemental, Follow up, DASII, Bikaner

Introduction

Jaundice is a yellowish discoloration of the skin and eyes caused by hyper-bilirubinemia.(1) Neonatal hyper-bilirubinemia is a common problem. Approximately 60% of term and 80% of preterm infants develop jaundice in the first week of life. High bilirubin levels may be toxic to the developing central nervous system and may cause neurological impairment even in term newborns. When total serum bilirubin exceeds 25mg/dl, infants are at risk for neurological damage. Unconjugated bilirubin is able to cross the blood-brain barrier and can accumulate in the brain leading to a number of possible adverse neurodevelopmental outcomes. Lethargy is common among infants with high total serum bilirubin levels, and as levels increase, auditory responses can diminish, and most severely, acute bilirubin encephalopathy or kernicterus can develop. Kernicterus is a form of chronic brain damage specifically caused by hyper-bilirubinemia, where the brainstem and basal ganglia are stained by bilirubin, accompanied by neurological deficits such as athetoid cerebral palsy, auditory dysfunction, or intellectual deficits.(2) The developing brain of premature babies is extremely vulnerable to injury; by increased level of bilirubin the risk for neurodevelopmental deficit increases with decreasing gestational age and birth weight resulting in relatively high risk of cerebral palsy, developmental delay, hearing and vision impairment and subnormal academic achievement. Similarly, small for date infants (birth weight <3rd centile) are also at significant risk of poor long term outcomes. Careful assessments of the risk factors involve a systematic approach to the detection and follow up of jaundice with the appropriate investigations and treatment so as to avoid complications.(3)

In order to prevent immediate and late neurological sequelae early detection of hyper-bilirubinemia & neurodevelopmental impairment is important to initiate the early intervention measures for better developmental outcome. The role of developmental assessment is to see that the child is progressing as per norms set by a large majority of children of the same age. It is by no means a predictor of future intelligent quotient and any deviation from the normal is brought to the notice of the parents, only in reassuring ways. The cause and effect relation between developmental deficits and risk factors can be much more complicated than we imagine. We cannot presume that neonatal jaundice will lead to mental retardation, fine and gross motor abnormalities, hearing loss and vision problems. But the risk of developmental disabilities is more in neonates exposed to hyper-bilirubinemia. The Preliminary analysis and statistics from many child, developmental centers and out-patient departments in hospitals have showed that babies with neonatal hyper-bilirubinemia have higher incidence of delayed developmental milestones and other associated problems, and many of these are reversible by early intervention.

Material and Methods

This prospective study was conducted at Sardar Patel Medical College, Bikaner (Rajasthan) from 2014 to 2015. The institutional committee was approved for this study. 115 newborns admitted in NICU (inborn + out born) with jaundice up to days of 7 were enrolled. The study criteria Includes: Neonates admitted in pediatric hospital with jaundice, requiring phototherapy/ exchange transfusion as per standard treatment guidelines, Gestational Age >34 weeks, birth weight >1.5 kg and excludes: Congenital anomalies, Gestational age <34 weeks, Sick Neonates having sepsis, neonatal seizures, birth asphyxia, hypothyroidism. Data about Birth history, gestational age, antenatal history, maternal history, total bilirubin level, day of onset, blood grouping, sepsis screening, risk factors, treatment given, and condition at discharge were collected in a predesigned Performa. At time of enrollment informed consent from parents was taken. At time of enrollment cases 'guardians were counseled. These newborns were examined at 3month and 12 month age and their neurodevelopmental assessment done by DASII method(Denver Developmental Screening test). In 115 cases, 17 cases were excluded because they did not turn, 2 cases were excluded due to CNS causes. Neurodevelopmental assessment was done and a composite DQ (motor and mental DQ) was calculated by DASII method. Both mental development index and psychomotor development index was calculated by DASII. The age placement of the item at the total score rank of the scale was noted as the child's developmental age. This converted the child's total scores to his motor age (MoA) and mental age(MeA). The respective ages were used to calculate his motor and mental development quotients respectively by comparing them with his chronological age and multiplying it by 100. All the collected data was tabulated and statically analyzed by using SPSS software.

Results

69.79% of hyper-bilirubinemic neonates were males & 30.21% were females. 27.08% were preterm (Gestational age <37 week) and 72.92% were term babies (≥37week). 50% neonates were having ≥2.5 kg birth weight. Peak serum bilirubin in 91.66% neonates was <25 mg/dl while 8.34% had levels ≥25 mg/dl. 51.04% hyper-bilirubinemic neonates had hemolytic and 48.96% had others etiology of jaundice. Majority(86.46%) of neonates were discharged within 3 days, only 13.54% had duration of stay more than 3 days. 71.17% hyper-bilirubinemic neonates were treated by phototherapy but 20.83% required exchange transfusion. The prevalence of neurodevelopmental abnormalities (DQ≤70) was 10.42% at 3 months where as it was 6.25% at 12 months follow up. 8.33% had motor & 10.42% had mental abnormalities at 3 months meaning thereby that in majority of patients motor abnormalities coexisted with mental abnormalities. Similar pattern was observed at 12 months where motor and mental abnormalities coexisted in all cases (6.25%). The association of peak serum bilirubin level ≥25 mg/dl with prevalence of neurodevelopmental abnormalities was found statistically significant (p<.05).

Table 1: Neurodevelopmental outcome at 3 and 12 months

Neurodevelopmental outcome	3 months		12 months	
	Cases	%	Cases	%
Normal(DQ>70)	86	89.58	90	93.75
Abnormal(DQ≤70)	10	10.42	6	6.25
Total	96	100	96	100

Table 2: Mean DQ at 3 & 12 months in relation to predictors of abnormal neurodevelopmental outcome

Peak serum bilirubin (mg/dl)	Mean DQ	
	3 months	12 months
<25 (n=88)	89.50+10.12	95.17+9.05
≥25 (n=8)	81.30+13.47	88.26+13.00
p value	0.035	0.049
Early onset of jaundice		
<1 day	75.49+9.79	85.20+12.90
>1 day	90.46+9.45	95.87+8.22
P value	.0001	.0001
Duration of hospital stay		
≤3 days	90.17+9.14	95.54+8.73
>3 days	81.31+14.88	90.60+11.38
P value	.004	.073
Treatment		
Exchange transfusion	78.65 ± 12.95	84.34 ± 12.27
phototherapy	91.79 ± 7.62	97.64 ± 5.67
P value	0.0001	0.0001

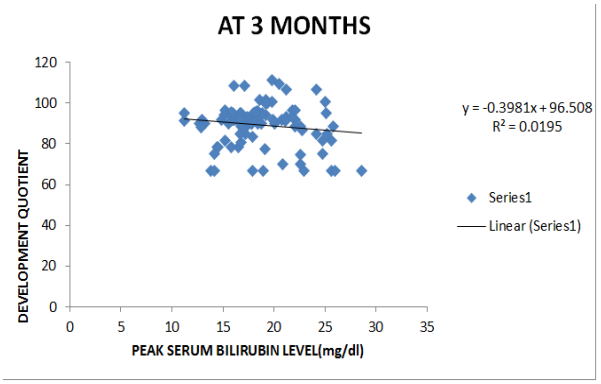

Fig. 1

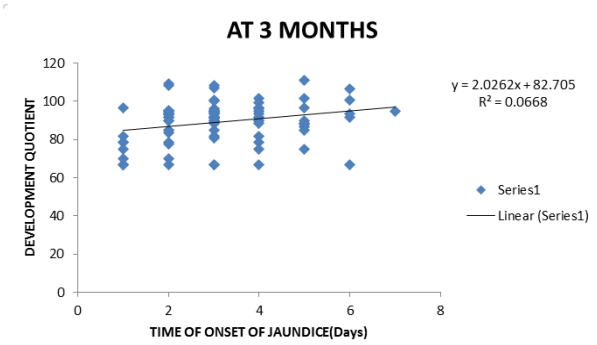

Fig. 2

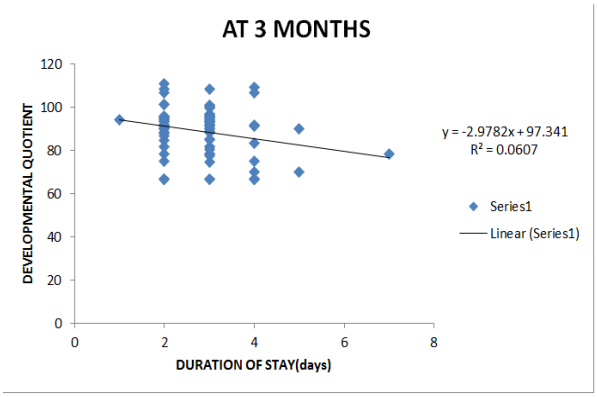

Fig. 3

Fig. 1, 2, 3: Linear regression analysis of predictors associated with abnormal neurodevelopmental outcome at 3 months

37%, and 25% cases with peak serum bilirubin level ≥ 25 mg/dl had abnormal DQ (≤70) at 3 and 12 months respectively as compared to 7.9% and 4.54% in those who had peak serum bilirubin <25 mg/dl. The association of peak serum bilirubin ≥25 mg/dl and mean DQ was significant at 3 and 12 months follow up. Mean DQ was lesser in neonates with high bilirubin level.[Table 2] Early onset of jaundice (≤1 day) was significantly associated with adverse neurodevelopmental outcomes (DQ≤70) at 3 and 12 months of age on follow up. Highly significant association of mean DQ was observed with day of onset of jaundice. Mean DQ in neonates with early onset of jaundice was significantly lesser.[Table 2] Highly significant association of duration of hospital stay was observed with abnormal DQ (≤70) at 3 months follow up. 38.46% babies with abnormal DQ(≤70) had >3 days hospital stay while only 6.02% cases with duration of stay ≤3 days had abnormal DQ(≤70)(p=.002). However this association was not found significant at 12 months follow up. Statistically significant association of mean DQ at 3 & 12 months of age was observed with hemolytic etiology of hyper-bilirubinemia. The prevalence of neurodevelopmental abnormalities was significantly greater in cases that had undergone exchange transfusion in comparison to neonates receiving only phototherapy. Mean DQ was significantly lower in neonates who required exchange transfusion. The association of these parameters (early onset of jaundice, serum bilirubin level>25 mg/dl and duration of hospital stay) with mean DQ was confirmed by logistic regression analysis.[Graph 1, 2, 3]

Discussion

Neonatal hyper-bilirubinemia is a common problem requiring medical attention in newborn and a leading cause of preventable brain damage, physical and mental handicap and early deaths among infants. Unconjugated hyper-bilirubinemia reflects a normal transitional phenomenon in most infants but in some, serum bilirubin levels rise to high levels causing neuro toxicity and subsequent death or lifelong neurological sequelae in surviving infants. The cause and effect relationship between neurodevelopment and risk factors of hyper-bilirubinemia is more complex and we cannot simply presume that neonatal hyper-bilirubinemia and presence of various risk factors will always lead to adverse neurodevelopmental outcome. Yet, because the neonatal hyper-bilirubinemia is a known, treatable risk factor so early detection and regular follow up for developmental abnormalities in these patients is important to initiate early intervention measures for better developmental outcome.

A total of 96 neonates with hyper-bilirubinemia, admitted to NICU and fulfilling the inclusion/exclusion criteria were included in the study and developmental evaluation was done at 3and 12 months by Developmental Assessment Scales for Indian Infants (DASII) method. This is a revision of 1970 Baroda Norms from birth to 30 months based on BSID RF 61, with indigenous material. Out of 96 hyper-bilirubinemic neonates enrolled in the study, 69.79% were males while 30.21% were females. 27.08% were preterm (gestational age <37 weeks) while the rest 72.91% were term (gestational age >37 weeks) deliveries. Birth weight of these hyper-bilirubinemic neonates were between 1.50 to 1.99 kg for 27.08%, 2.00 to 2.49 kg for 22.92% and >2.5kg for 50%. Peak serum bilirubin level of 91.66% neonates was below 25 mg/dl while 8.34 % cases were having peak level equal to or higher than 25 mg/dl. In our study, 9.38% cases had onset of jaundice within 24 hours of birth while in 90.62% cases, time of onset of jaundice was more than 24 hours of birth. 86.46% hyper-bilirubinemic neonates stayed in hospital for ≤3 days while in 13.54% hyper-bilirubinemic neonates; duration of stay was more than 3 days. Etiology for hyper-bilirubinemia was hemolytic in 51.04% cases (ABO, Rh, ABO+Rh, DCT positive) and non- hemolytic in the rest 48.96%. 79.17% hyper-bilirubinemic neonates received phototherapy while 20.83% cases required exchange transfusion.

In our study, the prevalence of abnormal neurodevelopmental outcome (DQ≤70, Developmental quotient) according to DASII method was 10.42% at 3 months which decreased to 6.25% on follow ups at 12

months suggesting that some component of neurodevelopmental abnormalities due to hyper-bilirubinemia could be transient or reversible. Similar decrease in prevalence has been reported by Chen et al (10.42% in hemolytic group and 2% in non-hemolytic group were neurodevelopmentaly abnormal at initial evaluation and returned to normal on follow up at 3 years).[4] Yilmaz et al in 2001 reported neurodevelopmental abnormalities in 11.5% cases in their study using DDST.[5] This prevalence is quite similar to the prevalence of neurodevelopmental abnormalities in our study (10.42%). The difference in the prevalence can be due to the difference in the used tools for developmental assessment, different ages for follow up and different socio-demographic factors and variables associated with hyper-bilirubinemia. Hymen et al reported that the prevalence of neurodevelopmental abnormalities was higher in hyper-bilirubinemic neonates with >20 mg/dl bilirubin levels.[6] In this study evaluation was done at 4 years of age. Prevalence of adverse neurodevelopment outcome (6.25%) at 1 year in our study was quite similar to that reported by Grunebaum et al.[7] Wolf et al[8] in 1999 reported that 23% cases were neurodevelopmentaly abnormal in their study by using BSID (Bayley's Scales for Infant Development) at 1 year of age and 12% were with abnormal motor outcome. Newman et al[9] in 2006 found in their study that 17% cases of hyper-bilirubinemia had abnormal neurological findings.

Soorani and Lunsing et al found abnormal neurological condition in 55% cases at 3 months of age according to assessed by observations of general movement, and 50% at 1 year of age according to Touwen assessment. On further evaluation these values decreased at 6 and 12 months as abnormal motor and abnormal mental outcome was 6.25% at 6 & 12 months.[10] Rosta et al found 5% cases having lower IQ at 8 year in their study.[11] We analysed the relation of various demographic factors and risk factors of hyper-bilirubinemia on neurodevelopmental outcome.

Mean DQ in male neonates was also not statistically different to the mean DQ observed in female neonates. Out of 70 hyper-bilirubinemic neonates with gestational age ≥37 weeks, 8(11.42%) and 2(7.14%) were abnormal (DQ≤70) at 3 and 12 month. Out of 26 cases with gestational age ≥37 weeks 2 (7.69%) and 1(3.84%) were neurodevelopmentaly abnormal rat 3 and 12 month of age. The difference in prevalence in relation to gestational age not found significant. In contrast to these, other studies like Scheidt et al[12] reported significant relationship of gestational age and neurodevelopmental abnormalities which were more in babies with low gestational age, Wolf et al reported that neurodevelopmental abnormalities were more in those hyper-bilirubinemic neonates who were having lower gestational age.[8] Prevalence of abnormal neurodevelopmental outcome in neonates having peak serum bilirubin (PSB) >25mg/dl was 37.5% and 25% in follow ups at 3 months and 12 months. The prevalence was observed to be lower in those having PSB < 25 mg/dl which was 7.95% at 3 months, and 4.54% at 12 months. The difference in both groups was significant at 3 months (p=0.008) as well as 12 months (p=0.022). A similar study have supported this conclusion.[13] The significant association between time of onset of jaundice and abnormal neurodevelopmental outcome has also been reported by Babu et al.[14] A study by Oh et al found PSB concentration during the first 2weeks of life directly correlated with Neurodevelopmental impairment.[15] In our study early onset of jaundice significantly associated with abnormal neurodevelopment. A longer duration of hospital stay was found to be positively associated with neurological abnormalities. We compared the mean DQ at all follow ups between the two groups and observed a significant association between mean DQ and duration of hospital stay at 3months (p=0.004) but not at 12 months (p=0.073). Nilson et al also supported this that longer duration of hospital stay is associated with lower IQ.[16]

We noticed a significantly higher prevalence of neurodevelopmental abnormalities in those who required exchange transfusion as compared to those who received phototherapy. Amongst those cases who required exchange transfusion, 45% and 25% were found to have abnormal neurodevelopmental outcome (DQ≤70) on evaluation at 3 and 12 months whereas only 1.31% of those who received phototherapy were found to have abnormal neurodevelopmental outcome (DQ≤70) at 3 month & 12 months. Difference in prevalence of abnormal neurodevelopmental outcome in both groups was statistically significant on evaluation at 3months (p=0.0001) and 12 months (p=0.001). Mean DQ was significantly lesser in those cases who required exchange transfusion on evaluation at 3 months (p=.001) and 12 months (p=.0001) as compared to those cases who received phototherapy. The hyperbilirubinemic neonates who were having hemolytic etiology, the prevalence of abnormal neurodevelopmental outcome (DQ ≤70) was higher (16.33% at 3 month, 10.20% at 12 months) as compared to those neonates who were having non hemolytic etiology (4.26% at 3 month, 2.13% at 12 months) in our study. Mean DQ was found significantly higher in non-hemolytic group than hemolytic group on evaluation at 3 & 12 months. (p=0.0001).

Conclusion

This Prospective observational study found a high prevalence of adverse neurodevelopmental outcome in neonates with hyper-bilirubinemia. Factors such as early onset & hemolytic etiology, longer duration of hospital stay, peak serum bilirubin level >25 mg/dl and need for exchange transfusion were significantly associated with adverse neurodevelopmental outcome as assessed by Developmental Assessment Scales for

Indian Infants (DASII). The prevalence of neurodevelopmental abnormalities was lesser at 12 months evaluation in comparison to prevalence at 3 months, signifying that neurodevelopmental abnormalities due to hyper-bilirubinemia are partially reversible. This finding underscores the importance of early detection of neurodevelopmental abnormalities and initiation of early intervention measures to reduce the prevalence of neurodevelopmental abnormalities in hyper-bilirubinemic neonates.

References

1. http://www.merckmanuals.com/professional/pediatrics/metabolic_electrolyte_and_toxic_disorders_in_neonates/neonatal_hyperbilirubinemia.html.
2. Maisels MJ, Baltz RD, Bhutani VK. Management of Hyper-bilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics 2004;114(1):297-316.
3. Follow up protocol - WHO newborn CC http://www. newbornwhocc.org/pdf/Follow- up of High Risk Neonates 050508. Pdf.
4. Wong V, Chen WX, Wong KY. Short- and long-term outcome of severe neonatal non-hemolytic hyper-bilirubinemia. J Child Neurol. 2006;21(4):309-15.
5. Yilmaz Y, Karadeniz L, Yildiz F, Degirmenci SY, Say A. Neurological prognosis in term newborns with neonatal indirect hyper-bilirubinemia. Ind Pediatr 2001;38(2):165-8.
6. Hyman CB, Keaster J, Hanson V, et al. CNS abnormalities after neo-natal hemolytic disease or hyper-bilirubinemia. A prospective study of405 patients. Am J Dis Child. 1969;117:395–405.
7. Grunebaum E, Amir J, Merlob P, Mimouni M, Varsano I. Breast mild jaundice: natural history, familial incidence and late neurodevelop-mental outcome of the infant. Eur J Pediatr.1991;150:267–270.
8. Wolf MJ, Wolf B, Beunen G, Casaer P. Neurodevelopmental outcome at 1 year in Zimbabwean neonates with extreme hyper-bilirubinaemia. Eur J Pediatr.1999;158:111–114.
9. Newman TB, Klebanoff MA. Neonatal hyper-bilirubinemia and long-term outcome: another look at the Collaborative Perinatal Project.Pediatrics.1993;92:651–657.
10. Soorani-Lunsing I, Woltil HJA, hadders M. Are moderate degrees of hyper-bilirubinemia in healthy term neonates really safe for the brain? Pedaitr Res 2001;50:701-5.
11. Rosta J, Makoi Z, Bekefi D, et al. Neonatal pathologic jaundice: seven to nine years follow-up. Acta Paediatr Acad Sci Hung.1971;12:317–321.
12. Scheidt PC, Mellits ED, Hardy JB, Drage JS, Boggs TR. Toxicity to bilirubin in neonates: infant development during first year in relationto maximum neonatal serum bilirubin concentration. J Pediatr. 1977;91:292–297.
13. Ip S, Chung M, Kulig J, O'Brien R, Sege R, Glicken S. An evidence based review of important issues concerning neonatal hyper-bilirubinemia. Pediatrics 2004;114(1):130-153.
14. Babu TA, Vishnu BB, Joseph NM. Association between peak serum bilirubin and neurodevelopmental outcomes in term babies with hyper-bilirubinemia. Ind J Pediatr 2012:79(2):202-206.
15. Oh W, Tyson JE, Fanaroff AA, Vohr BR, Perritt R, Stoll BJ. Association between peak serum bilirubin and neurodevelopmental outcomes in extremely low birth weight infants. Pediatrics 2003;112(4):773.
16. Nilsen ST, Finne PH, Bergso P, Stammes O. Males with neonatal hyper-bilirubinemia examined at 18 years of age. Acta Pediatr Scand 1984;73:176-180.