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Original Article

Developmental delay in 3-month-old low birth weight infants with hyperbilirubinemia

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Abstract

Background Developmental delay may be due to a variety of factors occurring during the prenatal, perinatal, or postnatal periods, one of which is hyperbilirubinemia.

Objective To evaluate the impact of hyperbilirubinemia on infant developmental delay.

Methods A prospective cohort study was conducted from March to July 2011. Subjects were low birth weight infants with and without hyperbilirubinemia. Developmental delay was measured using the *Mullen Scales of Early Learning*. Data was analyzed by Chi square test and relative risks were calculated. Logistic regression analysis was performed to assess factors associated with developmental delay. Differences were considered statistically significant for P values < 0.05.

Results Forty-six low birth weight infants were enrolled in this study, 23 with hyperbilirubinemia and 23 without hyperbilirubinemia. The relative risk (RR) for developmental delay in the hyperbilirubinemia group was 2.08 (95%CI 0.51 to 8.40). Multivariate analysis revealed that hyperbilirubinemia did not significantly influence developmental delay (RR 1.45; 95%CI 0.29 to 7.31). However, small for gestational age with or without hyperbilirubinemia significantly influenced developmental delay (RR 12.13; 95%CI 2.43 to 60.56).

Conclusion Hyperbilirubinemia in low birth weight infants is not a risk factor for developmental delay at the age of 3 months. However, being small for gestational age with or without hyperbilirubinemia significantly influences the likelihood of developmental delay. **[Paediatr Indones. 2013;53:228-31.]**

Keywords: *low birth weight infant, hyperbilirubinemia, developmental delay*

According to the 1991 Indonesian Health Demographic Survey (*Survey Demografi dan Kesehatan Indonesia*), the incidence of low birth weight (LBW) was 7.5%.[1] At Dr. Sardjito Hospital, the prevalence of newborn jaundice was 23.8%, defined as bilirubin levels increasing to >13 mg/dL. The incidence of jaundice in premature infants was 95% and that of hyperbilirubinemia was 56%.[2]

Hyperbilirubinemia and LBW are risk factors for developmental delay.[3] Hyperbilirubinemia in LBW babies is more severe and requires more intensive treatment compared to normal infants, due to immature red blood cells, liver, and gastrointestinal system.[4-6] Hyperbilirubinemia in LBW (< 2500 grams) is defined as serum bilirubin levels of > 5 mg/dL on first day of life, > 8 mg/dL on the second day, > 10 mg/dL on the third day, and > 12 mg/dL on the fourth day.[7] Cognitive developmental delay in LBW infants is related to the level of reduced birth weight. Emotional and behavioral delays may also be present in infants with LBW.[8] Hyperbilirubinemia

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complications happen if unconjugated bilirubin enters the brain, causing brain damage. The blood brain barrier is the primary protection for brain, but bilirubin may reach the blood brain barrier, leading to bilirubin encephalopathy.[9] Bilirubin encephalopathy may be fatal, or cause neurological sequelae and hearing loss in surviving infants.[8] Bilirubin neurotoxicity may induce dysfunction, ranging from mild cognitive impairment and hyperkinesis to severe sequelae.[10]

We aimed to evaluate the risk of developmental delay in low birth weight infants with and without hyperbilirubinemia, at the age of 3 months.

Methods

We performed a prospective, cohort study in the Perinatology Ward at Sanglah Hospital from March to July 2011. We screened all infants with LBW. Inclusion criteria were hyperbilirubinemia in the first 6 days of life, Denpasar resident, and availability of parental informed consent. We excluded infants with intracranial infection, head injury, brain tumor, radiation exposure during pregnancy, or genetic abnormalities. Reasons for dropping out of the study were neonatal seizure, parental refusal to join the study, or subjects moving to an unreachable address. Minimum sample size was calculated to obtain 80% power, 5% significance level ($P<0.05$), and 3.0 clinical differences. There were 46 LBW infants, 23 with hyperbilirubinemia and 23 without hyperbilirubinemia. Developmental delay was measured using the *Mullen Scales of Early Learning*, *American Guidance Service* (AGS) *Edition*, as the primary outcome in our subjects at the age of 3 months, during a follow-up visit at the clinic. Parents were contacted for appointment times at the clinic. If a parent missed the appointment, the authors conducted a home visit.

Data was analyzed by bivariate (Chi square) and multivariate (multiple logistic regression) analyses. A P value of < 0.05 with 95% confidence interval (CI) was considered to be statistically significant. This study was approved by the Ethics Committee and Research Department of Udayana University Medical School/Sanglah General Hospital.

Results

Study subjects consisted of 46 LBW infants, 27 of which were female (58.7%). Median gestational age, head circumference, body length, and albumin level, as well as other basic characteristics of subjects are shown in **Table 1.** We found that hyperbilirubinemia

Table 1. Characteristics of study subjects with LBW

Characteristics	Hyperbilirubinemia (n=23)	Without hyperbilirubinemia (n=23)
Median gestational age (range), weeks	35.0 (32-40)	36.0 (34-39)
Premature, n	15	16
Full term, n	8	7
Median head circumference (range), cm	31.0 (28-33)	31.0 (29-33)
Median body length (range), cm	44.0 (39-48)	44.0 (40-48)
Male gender, n	14	13
No severe asphyxia, n	23	23
Median weight, grams (interquartile range)	2000.0 (1450-2400)	2250.0 (1800-2450)
Normal for gestational age, n	14	18
Small for gestational age, n	9	5
Median serum albumin level (range), g/dL	3.7 (3.0-4.1)	3.7 (2.5-4.7)

Table 2. Relative risk of developmental delay in LBW babies with hyperbilirubinemia

Variable	Developmental delay (n=17)	Normal development (n=35)	RR	95% CI	P value*
Hyperbilirubinemia, n	7	16			
Without hyperbilirubinemia, n	4	15	2.08	0.51 to 8.40	0.30

* Chi squre test

Table 3. Multivariate analysis (logistic regression) of factors associated with developmental delay at the age of 3 months

Variables	RR	95% CI	P value
Small for gestational age	12.13	2.43 to 60.56	0.02
Hyperbilirubinemia	1.45	0.29 to 7.31	0.65

was not a risk factor for developmental delay **(Table 2).** Further analysis by multivariate logistic regression test showed that small for gestational age was significantly associated with developmental delay, but hyperbilirubinemia was not **(Table 3).**

Discussion

Studies on the effect of hyperbilirubinemia on infant development have yielded inconsistent results. Developmental delay in premature infants with hyperbilirubinemia has been reported to be higher compared to that of normal infants.[7] The risk of gross motor delay was found to be increased in full term babies with hyperbilirubinemia.[11] Hyperbilirubinemia was also found to be a risk factor for developmental delay at the age of 3 months, but prematurity and LBW were not.[12]

Hyperbilirubinemia may cause delayed development when a large amount of unconjugated bilirubin in the blood passes through the blood brain barrier, then conjugates with the brain phospolipid membrane, causing neuron damage.[13] Bilirubin also elicits neuroexcitatory signals and nerve conduction, especially in the auditory nerve, leading to neural hearing loss and impaired or delayed speech.[14] Bilirubin concentration and duration of exposure also worsened the damage.[8]

In our subjects, developmental delay was not influenced by hyperbilirubinemia. However, we found that the risk for developmental delay in LBW infants was 12 times higher in small for gestational age than in normal for gestational age infants. This result contrasts with that from a previous study perhaps due to different study design, measurement tools, and analysis.[11] Hyperbilirubinemia was found to not be a risk factor for autism in children.[15] In infants with hyperbilirubinemia whose development was later tested at the age of 3-5 years, no significant effect was observed. Also, there was no correlation between peak total serum bilirubin and hearing loss.[16] Furthermore, there was no relationship found between hyperbilirubinemia and delayed speech in premature children.[14] Satish *et al.* found no significant differences for gestational age, birth weight, serum albumin, and total bilirubin between normal babies and babies with hearing loss.[17]

We also found that hyperbilirubinemia was not a risk factor for developmental delay. However, albumin may alter the effects of bilirubin. If unconjugated bilirubin is totally bound to albumin, there would be no free bilirubin in the blood. Indirect bilirubin in fat could pass through the blood brain barrier by diffusion, particularly if albumin capacity to bind bilirubin and protein plasma was reduced. Therefore, albumin concentration in blood is strongly related to bilirubin in plasma.[14,18]

Multivariate analysis in our study revealed a significant difference in birth weight cateegories, as the risk of developmental delay at 3 months of age was higher in small for gestational age LBW subjects. Oh *et al.* found that the risk of developmental delay and health complications increased for LBW babies.[8] Bilirubin encephalopathy in LBW infants occurred at higher level bilirubin concentrations,[6,8] and these infants had poor prognoses (death). Those who survived had neurological impairments, such as developmental delay and hearing loss.[8]

A limitation of our study was that we did not measure the blood osmolality, which may influence bilirubin toxicity. Other factors potentially affecting development, such as stimulation, nutrition, environment, and prenatal factors also were not evaluated in our study. In addition, the sample population was limited to those residing in Denpasar, and measurement of developmental delay was performed only once. In conclusion, hyperbilirubinemia is not a risk factor for developmental delay in LBW infants, however, small gestational age with or without hyperbilirubinemia is a risk factor for developmental delay in our subjects at the age of 3 months.

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