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Original Article

Correlation between hyperbilirubinemia in term infants and developmental delay in 2- 4 year-old children

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Abstract

Background Up to 50 percent of term newborns have clinical jaundice during the first week of life. Many infants with bilirubin encephalopathy were asymptomatic, but they show neurodevelopmental delay few years later. Toxic effect occurs if unbound unconjugated bilirubin penetrates blood brain barrier and causes neuronal death.

Objective To investigate the relationship between moderate hyperbilirubinemia in term infants and developmental delay in 2 - 4 year old children.

Methods A retrospective cohort study was performed using medical record of infants born between 2006-2007 in Division of Neonatology Prof. R.D. Kandou General Hospital, Manado. Data from the medical record consisted of weeks of gestation, birth weight, Apgar scores, diagnosis of sepsis, congenital anomalies. Term infants with appropriate weight for gestational age were visited at their home to undergo developmental screening by Denver II and Vineland Social Maturity Scale test.

Results Fifty one children enrolled in this study (26 children with hyperbilirubinemia and 25 without hyperbilirubinemia) consisted of 27 boys and 24 girls. Most children were 24 – 29 months old (24/51). The results of Vineland Social Maturity Scale test showed 14 children had delayed social maturation (10 with history of hyperbilirubinemia). Denver II screening found 11 children had delayed language skill (10 with history of hyperbilirubinemia), 1 child with hyperbilirubinemia had delayed fine motoric and language skill.

Conclusions There is a relationship between moderate hyperbilirubinemia in term infants and developmental delay in 2 – 4 year old children. **[Paediatr Indones. 2010;50:154-58]**.

Keywords: *term infant, hyperbilirubinemia, developmental delayed*

Hyperbilirubinemia is one of the most common problems encountered in term newborns. Although up to 50 percent of term newborns have clinical jaundice during the first week of life, a few have significant underlying disease. Jaundice typically results from the deposition of unconjugated bilirubin pigment in the skin and mucous membranes. Neonatal hyperbilirubinemia is defined as a total serum bilirubin level above 5 mg/dl. Bilirubin, a heme catabolite, known for its potential toxicity to the neonatal central nervous system.[1-3]

Van de Bor[5] in her study on very low birth weight preterm infants reported that children with minor and major handicaps had significantly greater maximal serum total bilirubin concentration than those with normal neurodevelopmental outcome. At the age of 6 months, term infants with history of hyperbilirubinemia have increased gross motor skill delay.[6] A significant increase of minor neurologic dysfunction throughout the first year of life may be found in healthy infants with history of moderate

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hyperbilirubinemia.[7] Many infants with bilirubin encephalopathy were asymptomatic, but they showed neurodevelopmental delay few years later. The incidence of bilirubin encephalopathy in term infants may be as high as 2%.[8] Toxic effect occurs if unbound unconjugated bilirubin penetrates blood brain barrier and then binds to phospolipid and ganglioside of neuronal plasma membrane and finally causes neuronal death.[6]

Developmental delay is the outcome which is defined as a significant lag in the developmental sequences caused by brain defect which occur early in the brain development process. The initial disorder may occur during the prenatal, perinatal, or postnatal period. The milestone of development consists of gross motor skill, fine motor skill, as well as language and personal social skills.[9,10] The aim of this study was to find out the association between hyperbilirubinemia in term infants and developmental delay in 2 – 4 year old children.

Methods

This was a retrospective cohort study conducted in Prof. R. D. Kandou General Hospital from May until October 2009. Data on clinical and laboratory findings (total bilirubin serum, direct and indirect bilirubin, Apgar scores, gestational age, birth weight, sex, treatment for hyperbilirubinemia) were collected from medical records. We included children aged 2-4 years who were born full-term, with the birth weight of at least 2,500 g, total serum bilirubin level between 10–20 mg/dl, and gave parental informed consent to participate in this study. We excluded those with evidence of direct hyperbilirubinemia, congenital abnormalities, suffered from birth asphyxia, hypoglycemia, prolonged seizure, had a disease that could impair developmental milestone (meningitis, encephalitis, cerebral palsy), severe malnutrition, iron deficiency anemia, incomplete medical records. Subjects were recruited consecutively. As controls we included children born at term without hyperbilirubinemia.

Subjects were visited at their home; they underwent history taking, physical and laboratory examination. History taking, physical examination and Denver II examination were done by the authors. Vineland Social Maturity Scale test was done by a psychologist. Laboratory examination was done by clinical pathologist and the authors, assisted by skilled laboratory technician. Data collected included gender, age, education and occupation of parents/guardians, birth weight, mode of birth, history of illness/hospitalization, seizure, basic immunization, exclusive breast feeding, history of hyperbilirubinemia and its treatment. Physical examination of body weight, height, physiological and pathological reflexes, were carried out and recorded. Blood specimens were taken by an experienced technician for routine blood test.

We defined full-term infants as babies born at 37 – 42 week gestation.[11] Premature was defined based on gestational aged < 37 weeks, while appropriate for gestational age determined based on birth weight, i.e., 2.500 g – 4.000 g.[11] Asphyxia was defined as Apgar score of < 3 at 5 minute after birth. Hyperbilirubinemia was defined as total serum bilirubin > 10 mg/dl, direct hyperbilirubinemia defined as conjugated bilirubin > 2 mg/dl and or more than 15% from total serum bilirubin.[13] Developmental delay was defined if the child cannot complete test according to age based on Denver II (items are scored as either passed or failed, and profile scores are interpreted as being normal : no delay or < 1 caution, suspect : > 1 delay and/or > 2 caution or unstable in accordance with the number of passes in each of the four area) and Vineland Social Maturity Scale (defined as immature social maturity when social quotient < chronological age).[14,15] Duration of hyperbilirubinemia was determined by days of hyperbilirubinemia, counted from the first day when total serum bilirubin was 10-20 mg/dl and the last day when total serum bilirubin was < 5 mg/dl, total serum bilirubin tested based on clinical examination. Nutritional status was determined based on body weight compared to body height patients plotted on the WHO Z Scores curve according to their age and sex, if the result > 3 : obese, > 2 - < -1 : normal, < -2 : mild malnutrition , and < -3 : severely wasted.[16] Iron deficiency anemia was defined if on physical examination the patient had pale conjunctiva, with hemoglobin level of < 11g/dl, hematocrit < 33%, and decreased of mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH),

and mean corpuscular hemoglobin concentration (MCHC) with red cell distribution width (RDW) > 17%. [17]

Sample size was estimated by using $\alpha = 0.05$, power = 80%, and predicted correlation of 0.35, yielding a minimum subjects of 50. For analysis, P value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 17 for windows. Comparison between study groups was performed with chi-square test. Relative risk was calculated to determine the association between hyperbilirubinemia (independent variable) and developmental delayed (dependent variable). A logistic regression analysis was performed to evaluate duration of hyperbilirubinemia and developmental delay.

Results

We studied 26 healthy children who were born at term, appropriate for gestational age with history of hyperbilirubinemia with total serum bilirubin 10-19 mg/dl. Control group consisted of 25 healthy children without history of hyperbilirubinemia and matched for gestational weight, age, parent's education and occupation, exclusive breast feeding, and basic immunization. Twenty four children were 24–29 months old, almost all had normal nutritional status, only 4% subjects had exclusive breast feeding, 76% mother's education were senior high school, and all mothers were housewifes (**Table 1**).

All infants with hyperbilirubinemia had phototherapy, 12 (24%) received 3 day phototherapy, 9 (18%) received 4 day phototherapy, 4(8%) had 5 day phototherapy, 1 (2%) had 6 day phototherapy. Univariate logistic regression test showed that duration of hyperbilirubinemia was correlated with developmental delay and social immaturity in 2 – 4 year old children (**Tables 2 and 3**).

Children with hyperbilirubinemia had developmental delay and only one without hyperbilirubinemia had developmental delay. Ten children had delayed language skills and one child had gross motor skill and language skill delay. The results of Vineland Social Maturity Scale test showed that there were 10 children with hyperbilirubinemia had social immaturity, and four children without hyperbilirubinemia also had social immaturity. A Pearson chi-square analysis found a statistically significant correlation between hyperbilirubinemia and developmental delayed (**Tables 4 and 5**).

Table 1. Characteristics of subjects

Subjects characteristics	Hyper-bilirubinemia n = 26	Without hyper-bilirubinemia n = 25
Age (months)		
24 – 29 months	14	10
30 – 35 months	9	10
36 – 41 months	1	3
42 – 47 months	1	2
Nutritional status		
normal	25	24
mild malnutrition	1	1
Exclusive breast feeding	2	2
Mother's education		
Elementary	2	2
Junior high school	2	2
Senior high school	20	19
University	2	2

Tabel 2. Correlation between duration of hyperbilirubinemia and developmental delay by Denver II screening

Variable	Coefficient	P
Constant	-3.033	1.945
Duration of hyperbilirubinemia	0.666	0.048

Tabel 3. Correlation between duration of hyperbilirubinemia and social **immaturity** by Vineland Social Maturity Scale test

Variable	Coefficient	P
Constant	-1.722	0.001
Duration of Hyperbilirubinemia	0.339	0.045

Tabel 4. Association between hyperbilirubinemia with developmental delay by Denver II screening test

	Development		Pearson chi-square	P
	Normal	Delayed		
With hyperbilirubinemia	16	10		
Without hyperbilirubinemia	24	1		
Total	40	11	8.947	0.001

RR 9,6 (95%CI: 2.2 ; 42.7)

Tabel 5. Association between hyperbilirubinemia and social immaturity by Vineland Social Maturity Scale test

	Development		Pearson Chi square	P
	Normal	delayed		
Hyperbilirubinemia	16	21		
Without hyperbilirubinemia	10	4		
Total	26	25	3.229	0.035

Discussion

Before 1990, kernicterus in the previously healthy term infants was extraordinally rare and for most pediatricians it was a disease they unlikely found in their practice lifetimes. Since 1990, there has been an increase in the number of reported cases of kernicterus in United States. The primary concern with hyperbilirubinemia is the potential neurotoxicity effects, bilirubin inhibits mitochondrial enzymes, interfere with DNA synthesis, induces DNA-strand breakage and inhibits protein synthesis and phosporylation.[4,18]

Study of Yilmaz et al[19], found that in children aged 32 – 48 months, with hyperbilirubinemia less than 2 days showed normal developmental milestone, but 18.6% children, with hyperbilirubinemia more than 4 days, had a developmental delay. Nilsen et al[20] found a lower IQ score in children with total serum bilirubin > 15 mg/dl lasting more than 5 days. Ozmert et al[21] found that children with longer duration of hyperbilirubinemia would have neurodevelopmental delay. There were 51 children enrolled in this study, 26 children with history of hyperbilirubinemia and 25 without.

Bilirubin has neurotoxic effects. Adverse events of hyperbilirubinemia depends on severity of hyperbilirubinemia, duration of exposure (high bilirubin level with low duration of exposure or low bilirubin level with long duration of exposure).[22] In this study, the total serum bilirubin was 10 – 20 mg/dl (moderate hyperbilirubinemia). Low bilirubin level with long duration of exposure with neuronal cell had a significant correlation with developmental delay. At this time, it is not clear which one is more important in correlation with neurotoxicity: brief exposure to high bilirubin concentrations, or prolonged exposure to moderate concentrations[19]. In this study, logistic regression analysis found that correlation between duration of hyperbilirubinemia and developmental delay by Denver II examination was statistically significant (P = 0,048). So was the correlation between duration of hyperbilirubinemia and social immaturity by Vineland Social Maturity Scale (P = 0,045).

The mechanism for preferential localization of bilirubin to the basal ganglia in kernicterus is still unknown. Bilirubin appears to distribute differentially to brain subcellular compartments and is oxidized in brain by an enzyme localized on the inner mitochondrial membrane. This enzyme is found both in neurons and in glia, but appears to be more active in the latter.[23]

The Denver II Developmental Screening Test consists of up to 125 items, divided into four parts, i.e, social/personal (aspects of socialization inside and outside the home); fine motor function (eye/hand coordination and manipulation of small objects); language (production of sounds, ability to recognize, understand and use of language); gross motor functions (motor control, sitting, walking, jumping and other movements).[24,25] Ten children with history of hyperbilirubinemia had a language skill delay compared to 1 child without history of hyperbilirubinemia. The auditory system is thought to be the most sensitive neural systems to bilirubin-induced toxicity. Bilirubin induced auditory toxicity may depend on the degree and duration of indirect hyperbilirubinemia, may affect language development through its effect on the auditory nervous system.[26] In this study, the results of Pearson chi-square analysis showed that there was a significant correlation between hyperbilirubinemia in term infants and developmental delay by Denver II examination with P = 0.001, and relative risks was 9.6 (95% CI: 2.2; 42,7).

Vineland Social Maturity scale consists of 8 subscales, i.e, communication skills, general self help ability, locomotion skills, occupation skills, self direction, self help eating, self help dressing, socialization skills.[27] Pearson chi-square analysis found that there was a significant correlation between hyperbilirubinemia and social immaturity (performed by a psychologist) by Vineland Social Maturity Scale test with P = 0.035.

We concluded that there is an association between hyperbilirubinemia in term infants and developmental delay. The longer duration of hyperbilirubinemia and the longer duration of exposure of bilirubin to neuronal cell, the more significant the developmental delay.

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