Original Article

Neurological impairment of children with history of prematurity and neonatal hyperbilirubinemia

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ABSTRACT

Background In premature infants, the incidence of hyperbilirubinemia is still high. Bilirubin encephalopathy can develop without marked hyperbilirubinemia.

Objective To know the incidence of neurological impairment in premature with hyperbilirubinemia and the association between neurological impairment and serum unconjugated billirubin concentration.

Methods A retrospective study was conducted on 54 prematures with history of hyperbilirubinemia and 54 without history of hyperbilirubinemia born between 1997 and 1998 and discharged from Sanglah Hospital. Consecutive sampling was done. After univariate analysis, multivariate analysis was used to identify the association between serum unconjugated bilirubin concentration and neurological impairment at the adjusted age of ³18 months.

Results There were statistically significant differences in mean of age and neurological impairment between subjects with and without hyperbilirubinemia (p<0.0001 and 0.026). In subjects with hyperbilirubinemia, univariate analysis showed significant differences in means of serum unconjugated bilirubin concentration, gestational age, birth weight, and serum albumin concentration between subject who had neurological impairment and who had no neurological impairment with p = 0.005; 0.001; 0.002; <0.0001, respectively. Multivariate analysis found there were association between neurological impairment and serum unconjugated bilirubin concentration, gestational age, and serum albumin concentration with p<0.0001; 0.004; and <0.0001, respectively.

Conclusion Neurological impairment in subject with hyperbilirubinemia was greater than subject without hyperbilirubinemia. Serum unconjugated bilirubin concentration is one of three factors that associated with neurological impairment **[Paediatr Indones 2003;43:59-65].**

Keywords: children, neurological impairment, premature, hyperbilirubinemia

The incidence of hyperbilirubinemia in premature infants is still high. Monintja (quoted from Ismail[1]) reported that its incidence was 43%. The complication of hyperbilirubinemia is bilirubin encephalopathy or kernicterus attributable to the neurotoxicity of unconjugated bilirubin. Toxic effect of unconjugated bilirubin occurs when unbound unconjugated bilirubin passes through the blood brain barrier (BBB), binds to phospholipid and ganglioside of neuronal plasma membrane and finally causes neuronal death.[2-5] In premature infants, bilirubin encephalopathy can develop without marked hyperbilirubinemia.[6] Some investigators reported various incidence of bilirubin encephalopathy. Ahdab-Barmada *et al* (quoted from Volpe[5], Connolly[7], Menkes[8]) reported the incidence of bilirubin encephalopathy in premature infants was 25%. Wolf *et al*[9] demonstrated that 22% of neonates with hyperbilirubinemia develop bilirubin encephalopathy. Wilson-Castello [10] in a case control study reported that 33.3% of children with neurological impairment had a history of hyperbilirubinemia in the neonatal period. On the other hand, the neurological impairment of premature infants without hyperbilirubinemia was 6-9%.[11]

Concomitant with the increase of the quality of neonatal care, life expectancy of premature infants with hyperbilirubinemia is also increased. On the other hand, disability that emerges can produce serious problems for their family. Motivated by the known neurotoxicity of unconjugated bilirubin and serious problems that occurred, we conducted a study to know the incidence of neurological impairment and their association with serum unconjugated bilirubin concentration in the neonatal period.

Methods

The samples were derived from medical record of Neonatology Division at Sanglah Hospital Denpasar who were born between January 1997 and January 1998. Consecutive sampling was done to get 108 subjects. All subjects had ≥18 months of corrected age and prematurity history with 30-37 week gestational age The sample consisted of 54 children with history of hyperbilirubinemia and 54 children without history of hyperbilirubinemia in the neonatal period. Gender was matched, but gestational age, birth weight, and age were compared in both groups. Confounding variables such as toxemia gravidarum, abdomen X-ray during pregnancy, fetal distress, asphyxia, respiratory distress syndrome, hypoglycemia (blood sugar <20 mg/dL), congenital anomalies, sepsis, meningitis, encephalitis, seizure >15 minutes, operative delivery, partus praesipitatus, intracranial bleeding, head injury, malnourished, microcephaly, macrocephaly, and heart failure were excluded. Home visit was done for all cases that were eligible for this study. Confounding variables were also derived by questionnaire at the time of home visit. In the hyperbilirubinemic group, serum unconjugated bilirubin concentration, gestational age, birth weight, serum albumin concentrations, gender, and age between subjects who had neurological impairment and who had no neurological impairment were compared. Hyperbilirubinemia was defined as serum unconjugated bilirubin concentration >10 mg/dL. Gestational age was defined based on Dubowitz score. Neurological impairment was defined as one or more of the following: cerebral palsy, hearing loss, and strabismus. Cerebral palsy was established if we found 4 of 6 Levine's criteria, and there were no evidence of progressive neurological impairment. Hearing loss was defined as the absence of response to paper friction rub to both side ears.

Chi-square test was used to compare categorical variables, and two-tailed t test to compare continuous variables. Variables with $p < 0.05$ in univariate analysis were entered into multiple regression analysis. A p value of < 0.005 was considered to be significant.

TABLE 1. DISTRIBUTION OF NEUROLOGICAL IMPAIRMENT IN SUBJECT WITH AND WITHOUT NEONATAL HYPERBILIRUBINEMIA HISTORY

	Neurological impairment		Total	RR
	+ n (%)	- n (%)	n (%)	(95%CI)
Hyperbilirubinemia (+)	9 (17)	45 (83)	54 (100)	4.5
Hyperbilirubinemia (-)	2 (4)	52 (96)	54 (100)	(1.019;19.868)
Total	11 (10.2)	97 (89.8)	108 (100)	
$X^2 = 4.960$	df = 1	p = 0.026		

TABLE 2. CHARACTERISTICS OF SUBJECT WITH AND WITHOUT HISTORY OF NEONATAL HYPERBILIRUBINEMIA

Characteristics	Neonatal hyperbilirubinemia		t	p	95%CI
	+	-			
Age (mo)	47.0 (SD 2.8)	50.7 (SD 1.1)	-8.73	0.000	-4.48;-2.82
Gestational of age (mo)	33.7 (SD 2.0)	33.8 (SD 1.8)	0.51	0.613	-0.91;0.54
Birth weight (g)	2000.2 (SD 260.1)	2031.6 (SD 278.4)	-0.61	0.546	-134.18;71.41
Male (%)	28 (51.9)	28 (51.9)			

Results

From July 2000 to July 2001, there were 136 cases who visited our hospital. Twenty eight subjects were lost to follow up, 25 because their addresses were not found, 2 children died, and one refused to join. There were statistically significant differences in neurological impairment between the subjects with and without history of neonatal hyperbilirubinemia (**Table 1**). The relative risk was 4.5 (95%CI 1.02;19.87). Of nine subjects who had neurological impairment in the hyperbilirubinemic group, 8 had cerebral palsy, 3 had hearing loss, and 3 had strabismus. All subjects who had hearing loss and 2 subjects who had strabismus also had cerebral palsy. Both subjects with neurological impairment in non-hyperbilirubinemic group had cerebral palsy.

Table 2 shows the characteristics of subjects in both groups. There was a statistically significant difference in the mean of age between both groups, but no significant difference in gestational age and birth weight.

In subjects with history of neonatal hyperbilirubinemia (**Table 3**), there were statistically significant differences in the means of serum unconjugated bilirubin concentration, gestational age, birth weight, and serum albumin concentration between subjects who had neurological impairment and subjects who had no neurological impairment, but the mean age and gender were not statistically significant.

Multivariate analysis showed that neurological impairment was significantly associated with serum unconjugated bilirubin concentration, gestational age, and serum albumin concentration; but not with birth weight. About 56.1% of the neurological impairment was associated with serum unconjugated bilirubin concentration, gestational age, serum albumin concentration, and birth weight.

Discussion

Kernicterus is the term used to describe yellow staining of the basal ganglia and nuclear areas of the brain in newborn infants dying with severe jaundice. Bilirubin encephalopathy is also used (interchangeably with

TABLE 3. CHARACTERISTICS OF SUBJECT WITH NEONATAL HYPERBILIRUBINEMIA HISTORY WHO HAD AND WHO DID NOT HAVE NEUROLOGICAL IMPAIRMENT

Characteristics	Neonatal hyperbilirubinemia				
	Neurological impairment (+)	Neurological impairment (-)	t	p	95%CI
Mean UB (mg/dL)*	16.8 (SD2.4)	14.4 (SD 2.3)	2.94	0.005	0.78;4.41
Mean GA (mo)*	32.0 (SD 1.1)	34.0 (SD 2.0)	-4.14	0.001	-2.97;-0.98
Mean BW (g)*	1821.1 (SD 144.5)	2036.0 (SD 264.3)	-3.57	0.002	-350.90;-92.21
Mean Alb (g/dL)*	2.7 (SD 0.2)	3.1 (SD 0.3)	-5.09	0.000	-0.62;-0.27
Mean age (mo)*	48.2 (SD 2.4)	46.8 (SD 3.1)	1.28	0.208	-0.80;3.60
Male (%)**	5 (55)	23 (51.1)	0.06	0.808	

Abbreviation :	UB	:Unconjugated bilirubin	GA	:Gestational of age
	BW	:Body weight	Alb	:Albumin
	*	:Analyzed by two-tailed *t* test	**	:Analyzed by Chi-square test

TABLE 4. MULTIVARIATE ANALYSIS OF ASSOCIATION BETWEEN CHARACTERISTICS OF SUBJECTS AND NEUROLOGICAL IMPAIRMENT

Characteristics	R²	*p*
UB (mg/dL)	0.561	<0.0001
GA (mo)		0.044
Alb (g/dL)		<0.0001
BW (g)		0.158

Abbreviation:	UB :Unconjugated bilirubin	GA	:Gestational of age
	Alb :Albumin	BW	:Birth weight

kernicterus) to describe an acute or chronic neurological syndrome that is believed to reflect bilirubin toxicity.[2]

Three conditions occurred when the brain is exposed to unconjugated bilirubin i.e., [1] without functional disturbances and clinical manifestations, [2] with reversible functional disturbance, and [3] disruption of structure and function of the brain. In premature infants, the third condition is the most common manifestation.

The clinical features of infants who have sustained bilirubin injury to their brain in the neonatal period depend upon the topography of the neuropathological findings and their interrelations with brain maturation. Because of these interrelations, the clinical features differ according to the age of the infants. [5,8] One study of the occurrence and nature of the clinical features of infants with marked hyperbilirubinemia who have either died with pathologically proven kernicterus or survived to develop the clinical syndrome of chronic bilirubin encephalopathy of the post kernicterus, reported that about 55-65% of cases with definite neurological signs, 20-30% with equivocal neurological signs, and 15% without definite neurological signs. [5] In our study, the incidence of neurological impairment in children with premature and neonatal hyperbilirubinemia was 17%. From the medical record we found that none of them showed acute clinical manifestations. This was associated with immaturity of the brain attributable to premature infants. Wolf *et al*[9] demonstrated that 22% of children with history of neonatal hyperbilirubinemia had neurological impairment. Ahdab-barmada *et al* (quoted from Connolly[7]) found the neurological impairment in children born premature with history of neonatal hyperbilirubinemia was 25%. In a case-control study, Wilson-Castello *et al*[10] reported that 33.3% of children with neurological impairment had history of neonatal hyperbilirubinemia. The different result of these studies may be due to the difference in cut off point of bilirubin concentration (10 mg/dL in our study and 23.4 mg/dL in Wolf's study), gestational age (25-34 weeks in Ahdab-Barmada's study and 30-37 weeks in our study), and the design of study (cohort retrospective in our study and case control in Wilson-Castello's study).

Neurological impairment occurs in premature or low birth weight infants due to immaturity of structure and function of organ especially the brain.[11-13]

On the other hand, clinical features of neurological impairment in children with history of neonatal hyperbilirubinemia are delayed in some cases. Clinical features become clearer in older than younger children. [7,14] The incidence of bilirubin encephalopathy is greater in male than female infants. [15,16] In our study, there were no statistically significant differences in the means of gestational age, birth weight and gender between subjects with and without history of neonatal hyperbilirubinemia. Although the mean age differed between the two groups (Table 2), the incidence of neurological impairment was not influenced. This was because the difference was not so large (± 3.7 months).

There are some important determinants of neuronal injury caused by bilirubin, including:[5,17] [1] concentration of serum-unconjugated bilirubin, [2] concentration of serum albumin, [3] bilirubin binding by albumin, [4] concentration of hydrogen ions-acidosis, [5] blood-brain barrier (BBB), and [6] neuron susceptibility. In premature or low birth weight infants, the permeability of BBB is increased due to immaturity. This is why the incidence of bilirubin encephalopathy was greater in the premature and low birth weight infants than that in full term infants.[5,17]

The correlation between neurotoxicity and elevation of serum-unconjugated bilirubin is not so great. Concentration of serum albumin is more important in determining the neurotoxicity of unconjugated bilirubin. At lower concentration of serum albumin, the overall reaction will favor formation of unbound bilirubin anion and ultimately bilirubin acid. Bilirubin acid is the toxic form of unconjugated bilirubin.[5] In the pathogenesis of bilirubin encephalopathy, the increased permeability of BBB is also important. In premature or low birth weight infants, the BBB is more permeable than full term infants.[6]

Usually the neurotoxicity effect of unconjugated bilirubin occurs when its level is more than 20 mg/dL.[3,6,18-24] In premature infants, bilirubin encephalopathy can develop without marked hyperbilirubinemia. This is due to incomplete formation of BBB and low serum albumin concentration.[6] There were negative correlation between the gestational age and the elevation of serum bilirubin concentration,[25-27] permeability of BBB;[6] and positive correlation between the gestational age and serum albumin concentration.[28] In our study, the mean of serum unconjugated

bilirubin concentration was greater, but the mean gestational age and serum albumin concentration was lower in subjects with neurological impairment than subjects without neurological impairment. This condition results in elevation of serum unbound bilirubin concentration and is accompanied by increased permeability of BBB, ultimately the probability of bilirubin encephalopathy was also increased. This result was confirmed by multivariate analysis and found that there were relationships between neurological impairment and the mean of serum unconjugated bilirubin concentration, serum albumin concentration, and gestational age. A collaborative perinatal case-control study[29] reported that 57 out of 61 (93.4%) children who had neurological impairment at 7 years of age had history of serum unconjugated bilirubin concentration of less than 10 mg/dL. This finding indicated that bilirubin encephalopathy has developed without marked hyperbilirubinemia. Delayed motor development in the first year was demonstrated in premature infants with moderate hyperbilirubinemia in the Collaborative Perinatal Project,[30] and a large prospective study of premature infants with follow up through age 2 years demonstrated a dose-response relationship between maximal neonatal bilirubin level and risk for impaired neurodevelopment outcome at 2 years.[31] Wolf *et al*[9] found 22% of neonates with hyperbilirubinemia develop bilirubin encephalopathy. Wilson-Castello *et al*[10] in a case-control study reported that 33.3% of children with neurological impairment had history of neonatal hyperbilirubinemia. On the other hand, a retrospective cohort study by O'Shea *et al*[32] in one year old (corrected age) children with very low birth weight history demonstrated that there was no relationship between hyperbilirubinemia and neurological impairment. This study was supported by Yeo *et al*[14] in a retrospective cohort study in neonates with hyperbilirubinemia who underwent phototherapy. They found that there was no relationship between hyperbilirubinemia and neurological impairment. The different results of these studies may be due to the difference in the age of subjects, gestational age, birth weight, serum unconjugated bilirubin concentration, serum albumin concentration, and study design. The onset of phototherapy was also an influencing factor.

Although there were no statistically significant differences in age and gender between subjects who had neurological impairment and who had no neurological impairment (Table 3), the clinical features were different. Currently the association between gender and neurological impairment is still unclear.

There is an association between birth weight and bilirubin encephalopathy.[5,7,8] This is associated with negative correlation between birth weight and permeability of BBB.[6] In multivariate analysis (Table 4), there was no association in both. This was because Dubowitz score determined gestational age subjectively.

Phototherapy is the most common mean of treatment of hyperbilirubinemia.[33] Phototherapy, by photoisomerization and photo oxidation, results in the formation of more polar, water-soluble bilirubin products.[19,28,33] The most important reaction appears to be the formation of lamirubin, a stable structural photo isomer. Lamirubin does not require conjugation,[33] and is rapidly excreted in bile and urine.[15,19,34] In our study, neurological impairment was found although the subjects had received phototherapy. This finding indicated that the brain had been exposed to unconjugated bilirubin for 2 hours or more at the initiation of phototherapy.[35] This problem may be caused by some factors such as late initiation of photo therapy attributable to limitation of photo therapy facilities, poor light quality due to the use of the light more than 2000 hours, and delay to establish diagnosis of hyperbilirubinemia.

Though we found that there was a relationship between hyperbilirubinemia and neurological impairment, a prospective cohort study needs to be done because there might be recall bias in a retrospective study.

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