The Turkish Journal of Pediatrics 1996; 38: 199-204

THE RISK OF BILIRUBIN ENCEPHALOPATHY IN NEONATAL HYPERBILIRUBINEMIA*

*Remzi Oktay MD***, *Mehmet Satar MD****, *Aytuğ Atıcı MD*****

SUMMARY: Oktay R, Satar M, Atıcı A. (Neonatology Unit, Department of Pediatrics, Çukurova University Faculty of Medicine, Adana, Turkey). The risk of bilirubin encephalopathy in neonatal hyperbilirubinemia. Turk J Pediatr 1996; 38: 199-204.

Jaundice is the most common and one of the most annoying problems that can occur in the newborn. Although most jaundiced infants recover without any serious problem, there is always a risk of bilirubin encephalopathy during the period of hyperbilirubinemia.

The relationship between encephalopathy and serum free bilirubin levels was investigated in 83 newborn infants (40 premature, 43 mature) with unconjugated hyperbilirubinemia. A complete physical examination was done in all patients, and signs of bilirubin encephalopathy were noted if present. The serum free bilirubin level exceeded 0.1 mg/dl in 13 infants, and 12 of them showed signs of encephalopathy. On the other hand, none of the infants whose serum free bilirubin levels were below 0.1 mg/dl showed signs of encephalopathy.

Although there is a significant positive correlation between serum total and free bilirubin levels, it is not clear at what total bilirubin level free bilirubin will appear. Serial determinations of free bilirubin appear to be more helpful in the management of hyperbilirubinemia in infants with an increased risk of bilirubin toxicity. *Key words: encephalopathy, free bilirubin, jaundice, neonatal hyperbilirubinemia.*

Hyperbilirubinemia is one of the most common problems during the neonatal period, and the risk of bilirubin encephalopathy was first recognized many years ago. Bilirubin encephalopathy is a neurologic syndrome resulting from the deposition of bilirubin in brain cells. The precise blood level above which indirect-reacting bilirubin or free bilirubin will be toxic for an individual infant is unpredictable[1-4].

Several studies have suggested that there is a relationship between bilirubin encephalopathy and serum free bilirubin levels, but it has also been reported that albumin-bound bilirubin may cause bilirubin encephalopathy in cases of acute blood-brain barrier damage. Many of the biochemical and physiological factors involved in the pathogenesis of bilirubin encephalopathy have been identified during recent years, but their relative importance remains unclear[4-6].

The aim of this prospective study was to investigate the relationship between bilirubin encephalopathy and serum free bilirubin levels in neonatal hyperbilirubinemia.

* From the Neonatology Unit, Department of Pediatrics, Çukurova University Faculty of Medicine, Adana.

** Pediatrician, Çukurova University Faculty of Medicine.

*** Associate Professor of Pediatrics, Çukurova University Faculty of Medicine.

**** Assistant Professor of Pediatrics, Çukurova University Faculty of Medicine.

Material and Methods

Çukurova University Medical Faculty Research Hospital is one of the main referral centers in south and southeast Turkey for the management of neonatal hyperbilirubinemia. A total of 83 newborns who were referred to us with unconjugated hyperbilirubinemia formed the study group.

A detailed history was obtained in all cases, and a complete physical examination was done by an experienced pediatrician working in the field of neonatology. Signs of bilirubin encephalopathy, such as lethargy, irritability, poor sucking, hypertonia and high-pitched cry were noted if present[4,6]. Other possible reasons for these symptoms (hypoglycemia, systemic infection, intracranial hemorrhage, etc.) were carefully evaluated.

The gestational age of each patient was calculated from the mother's last normal menstrual period or by using the Dubowitz method[7]. Forty of the 83 infants were premature, and the remainder were term, with a mean gestational age of 34.9 ± 2.0 and 39.3 ± 1.2 weeks, respectively.

Total and direct bilirubin concentrations and serum albumin levels were determined by using Technicon RA-XT (England). Sephadex G-25 gel filtration method, which was modified by Blondheim et al.[8], was used to determine the patients' serum free bilirubin levels.

The collected data was evaluated using the SPSS-X (Rel. 4.1) package program. The statistical analyses were done with Student t, Mann Whitney U and correlation coefficient tests.

Results

The characteristics of the mature and premature infants are shown in Table I. The mean albumin and total, direct and free bilirubin levels were not different in the premature and mature groups ($p > 0.05$) (Table II).

Table I: Selected characteristics of the Infants

		Premature	Mature
Sex	Female	13	21
	Male	27	22
	Total	40	43
Gestational age (weeks) (Mean ± SD)		30-37 (34.9 ± 2.0)	38-42 (39.3 ± 1.2)
Birth weight (grams) (Mean ± SD)		1330-4000 (2515 ± 579)	2455-4850 (3292 ± 459)
Postnatal age (days) (Mean ± SD)		1-20 (6.5 ± 4.5)	1-11 (5.5 ± 2.3)

Table II: Mean Albumin; Total, Direct and Free Bilirubin Levels in Premature and Mature Infants

	Premature	Mature	p
Number of infants	40	43	
Total bilirubin (mg/dl) (Mean ± SD)	7.2-33.6 (20.2 ± 5.4)	3.4-40.4 (20.7 ± 7.8)	> 0.05
Direct bilirubin (mg/dl) (Mean ± SD)	0.4-2.0 (1.06 ± 0.39)	0.4-2.0 (0.95 ± 0.35)	> 0.05
Albumin (g/dl) (Mean ± SD)	1.9-5.3 (3.7 ± 0.7)	2.9-5.0 (3.9 ± 0.5)	> 0.05
Free bilirubin (mg/dl) (Mean ± SD)	0.000-0.270 (0.043) ± 0.044)	0.000-0.660 (0.045 ± 0.122)	> 0.05

Free bilirubin was found in the sera of 27 premature (67.5%) and 15 mature (34.8%) infants. However, only six infants in the premature (15%) and six infants in the mature (13.9%) groups showed signs of encephalopathy on admission, and none of them subsequently developed encephalopathy. A significant positive correlation was found between serum total and free bilirubin levels ($r = 0.70$, $p < 0.01$). The mean total and free bilirubin levels were not different in premature and mature infants who showed signs of encephalopathy (Table III).

Table III: Mean Total and Free Bilirubin Levels in Infants with Encephalopathy

	Premature	Mature	p
Number of infants	6	6	
Total bilirubin (mg/dl) (Mean ± SD)	19.9-33.6 (27.1 ± 5.7)	18.5-40.4 (32.7 ± 8.4)	> 0.05
Free bilirubin (mg/dl) (Mean ± SD)	0.104-0.270 (0.173 ± 0.062)	0.108-0.660 (0.278 ± 0.220)	> 0.05

Serum free bilirubin was greater than 0.1 mg/dl in all of the infants who showed signs of encephalopathy, while only one of the normal infants had serum free bilirubin greater than this level. The serum total and free bilirubin levels of the patients are shown in Table IV, and these levels were significantly higher among patients with signs of encephalopathy.

Table IV: Serum Total and Free Bilirubin Levels in Patients with and without Encephalopathy

	Encephalopathy (+)	Encephalopathy (-)	p
Number of infants	12	71	
Free bilirubin (mg/dl) (Mean ± SD)	0.104-0.660 (0.225 ± 0.164)	0.000-0.112 (0.013 ± 0.022)	< 0.001
Total bilirubin (mg/dl) (Mean ± SD)	18.5-40.4 (29.9 ± 7.4)	3.4-29.9 (18.9 ± 5.1)	< 0.001

Discussion

The present study reviews our experience with neonatal hyperbilirubinemia and bilirubin encephalopathy. It is a well-known fact that free bilirubin has toxic effects on the brain, and that the amount of bilirubin entering the brain increases dramatically when total serum bilirubin levels exceed 20 mg/dl[1, 9-11]. The management of hyperbilirubinemia is usually based on serum total bilirubin levels in many centers. Although a significant positive correlation was found between serum total and free bilirubin levels, it is almost impossible to predict when free bilirubin which is directly toxic to the brain, will appear in the serum[8, 12, 13].

In general, prematurely born infants appear to be more susceptible than mature neonates to the development of bilirubin encephalopathy[14]. In the present study, premature infants seemed to have free bilirubin in their sera more frequently than term infants, although there were no differences between their serum total bilirubin and albumin levels. The lower binding capacity of albumin in premature infants may play a role in the increase in free bilirubin levels[15]. However, unexpectedly, the number of infants with signs of kernicterus was the same in the premature and mature groups.

It is well known that free bilirubin is not the only factor in the pathogenesis of bilirubin encephalopathy. Many of the biochemical, physiological, environmental and genetic factors that may play a role in the pathogenesis of bilirubin encephalopathy have been defined recently[4]. These include the binding of bilirubin to albumin, which increases with postnatal age, the transport and passage of bilirubin across the blood-brain barrier, and the susceptibility of the target neurons[4, 6]. The role of free fatty acids in altered bilirubin binding is still controversial[16]. Although the development of hyperbilirubinemia is reported to be more probable in neonates with high alpha-fetoprotein levels in the umbilical cord[17], the relationship between alpha-fetoprotein, the transferrin/alpha-fetoprotein ratio and hyperbilirubinemia is still under investigation[18, 19]. The duration of exposure to high concentrations of free bilirubin may also play a role in bilirubin encephalopathy, but it was impossible to predict this duration in the present study.

Makamura et al.[12] and Zamet et al.[13] reported that all the kernicteric infants in their study groups had serum free bilirubin levels greater than 0.1 mg/dl. Similarly, in the present study, we found 13 infants with serum free bilirubin levels exceeding 0.1 mg/dl, and 12 of them subsequently showed signs of encephalopathy. On the other hand, none of the infants whose serum free bilirubin levels were below 0.1 mg/dl showed signs of encephalopathy. A serum free bilirubin level exceeding 0.1 mg/dl seems to be a good indicator of a high risk for bilirubin encephalopathy.

Thus, we believe that serial free bilirubin measurements, in addition to assessment of the other risk factors mentioned above, would be helpful in the management of jaundiced infants at risk for bilirubin encephalopathy.

REFERENCES

1. Brodersen R. Binding of bilirubin to albumin. Crit Rev Clin Lab Sci 1980; 11: 305-309.
2. Brodersen R, Stern L. Deposition of bilirubin acid in the central nervous system a hypothesis for the development of kernicterus. Acta Paediatr Scand 1990; 79: 12-19.
3. Deziel MR, Girotti AW. Photodynamic action of bilirubin on liposomes and erythrocyte membranes. J Biol Chem 1980; 255: 8192-8198.
4. Wennberg RP. Bilirubin physiology. In: Roberton NRC (ed). Textbook of Neonatology (2nd ed). London: Churchill Livingstone; 1992: 605-617.
5. Bratlid D. How bilirubin gets into the brain. Clin Perinatol 1990; 17: 449-465.
6. Gartner LM, Lee KS. Unconjugated hyperbilirubinemia. In: Fanaroff AA,Martin RJ (eds). Neonatal-Perinatal Medicine (5th ed). Missouri: Mosby-Year Book; 1992: 1075-1104.
7. Dubowitz L, Dubowitz V, Goldberg C. Clinical assessment of gestational age in the newborn infant. J Pediatr 1970; 77: 1-10.
8. Blondheim SH, Kapitulnik J, Valaes T. Use of a sephadex column to evaluate the bilirubin-binding capacity of the serum of infants with neonatal jaundice. Israel J Med Sci 1972; 8: 22-28.
9. Brodersen R. Bilirubin transport in the newborn infant, reviewed with relation to kernicterus. Pediatrics 1980; 96: 349-356.
10. Maisels MJ. Jaundice. In: Avery GB, Fletcher AM, McDonald MG (eds). Neonatology (4th ed). Philadelphia: JB Lippincott; 1994: 630-725.
11. Robinson PJ, Rapoport SI. Binding effect of albumin on uptake of bilirubin by brain. Pediatrics 1987; 79: 553-558.
12. Nakamura H. Lardinois R. Unbound bilirubin in icteric newborns. Biol Neonate 1972; 21: 400-417.
13. Zamet P, Chunga F. Separation by gel filtration and microdetermination of unbound bilirubin. II. Study of sera in icteric newborn infants. Acta Pediatr Scand 1971; 60: 33-38.
14. Gartner LM, Snyder RN, Chabon RS. Kernicterus: high incidence in premature infants with low serum bilirubin concentrations. Pediatrics 1970; 45: 906-917.
15. Hansen TW, Bratlid D. Bilirubin and brain toxicity. Acta Paediatr Scand 1986; 75: 513-522.
16. Ostrea EM Jr, Bassel M, Fleury CA, et al. Influence of free fatty acids and glucose infusion on serum bilirubin and bilirubin binding to albumin: clinical implications. J Pediatr 1983; 102: 426-432.

17. Hodr R, Stroufova A, Kepertova M, Ondrackova Z, Skutilova J. Alpha-fetoprotein in umbilical cord blood and hyperbilirubinemia in normal neonates. Cesk Pediatr 1990; 45: 390-393 (Eng. Abstr.).

18. Montagna O, Mautone A, Altomare M, et al. Transferrin/alpha-fetoprotein ratio as a predictive index in hyperbilirubinemia. Minerva Pediatr 1987; 39: 361-363 (Eng. Abst.).

19. Laszlo V, Kurcz M, Nagy I, Felszegi K. Serum alpha-fetoprotein patterns in the newborn with indirect hyperbilirubinemia. Orv Hetil 1985; 126: 507-508, 511-514 (Eng. Abstr.).