IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

Open Access
Original Article

Etiologies of Prolonged Unconjugated Hyperbilirubinemia in Neonates Admitted to Neonatal Wards

Mohammad Kazem Sabzehei[1], Behnaz Basiri[1], Zahra Gohari[2], Hassan Bazmamoun[1]*

1. Department of Pediatrics, Besat Hospital, Hamadan University of Medical Sciences, Hamadan, Iran
2. General Practitioner, Hamadan University of Medical Sciences, Hamadan, Iran

ABSTRACT

***Background*:** Jaundice is a common condition among neonates. Prolonged unconjugated hyperbilirubinemia occurs when jaundice persists beyond two weeks in term neonates and three weeks in preterm neonates. This study aimed to determine the etiologies of prolonged unconjugated hyperbilirubinemia in infants admitted to the neonatal ward of Besat Hospital in Hamadan, Iran.

***Methods*:** This study was conducted on all infants diagnosed with prolonged unconjugated hyperbilirubinemia during 2007-2012 in the neonatal ward of Besat Hospital in Hamadan, Iran. Demographic characteristics of infants, physical examination and laboratory findings were collected and analyzed to determine the etiologies of neonatal hyperbilirubinemia.

***Results*:** In total, 100 infants diagnosed with neonatal hyperbilirubinemia were enrolled in this study, including 49 male and 51 female neonates with mean age of 20±1 days and mean bilirubin level of 17.5±4.0 mg/dL. Main causes of hyperbilirubinemia were urinary tract infection, ABO incompatibility, hypothyroidism and glucose-6-phosphate dehydrogenase deficiency in 14%, 5%, 6% and 5% of neonates, respectively. Moreover, unknown etiologies, such as breastfeeding, were detected in 70% of the studied infants.

Conclusion: According to the results of this study, determining the main causes of prolonged unconjugated hyperbilirubinemia in neonates is of paramount importance. In the majority of cases, neonatal hyperbilirubinemia is associated with physiological factors, such as breastfeeding.

Keywords: Prolonged Unconjugated Hyperbilirubinemia, cholestasis, neonate

Introduction

Prolonged unconjugated hyperbilirubinemia is a type of neonatal jaundice, which occurs in infants with high bilirubin levels (>10 mg/dL) persisting beyond 14-21 days (1). Prolonged unconjugated hyperbilirubinemia is a common problem among newborns, and the prevalence rate has been estimated at 2-15%. Although this condition is normally manageable, it may sometimes be a sign of other serious diseases.

According to the literature, breastfeeding is a major cause of prolonged jaundice, and about 40% of infants who are exclusively breastfed are diagnosed with this disorder (2-5). Among other pathological causes associated with prolonged hyperbilirubinemia are urinary tract infection (UTI), congenital hypothyroidism and hemolysis. Therefore, these factors should be taken into account in the evaluation of neonates for jaundice. Early diagnosis and treatment of hyperbilirubinemia could prevent further complications in term and preterm infants.

According to statistics, incidence of UTI has been estimated at 7.5-8.2% in asymptomatic, afebrile, jaundiced neonates younger than 8 weeks of age (6-9). Congenital hypothyroidism is known as a major cause of prolonged jaundice in newborns, which may lead to several complications, such as mental retardation, in case of delayed treatment. It is noteworthy that characteristics of the clinical findings are reported in only 5% of infants with hyperbilirubinemia, and prolonged jaundice is diagnosed in 1-6.3% of these cases (10-12). As another contributing factor, hemolysis leads to the elevation of bilirubin level in neonates, and patients should be suspected of unconjugated hyperbilirubinemia if jaundice is prolonged beyond the first week of life (6-9, 13).

On the other hand, mutations in glucuronyl-transferase enzyme could lead to the development of prolonged jaundice; these mutations are usually manifested in conditions such as Crigler-Najjar syndrome and Gilbert's syndrome.

* *Corresponding author*: Hassan Bazmamoun, Department of Pediatrics, Besat Hospital, Hamadan University of Medical Sciences, Hamadan, Iran. Tel: 08132640062; E-mail: hbazmamoun@yahoo.com

This study aimed to evaluate the frequency of different etiologies and pathological causes associated with prolonged unconjugated hyperbilirubinemia in order to highlight the significance of work-up for neonates presented with prolonged jaundice.

Materials and Methods

This cross-sectional descriptive study was conducted on all the neonates diagnosed with prolonged unconjugated hyperbilirubinemia admitted to the neonatal ward of Besat Hospital in Hamadan, Iran during 2007-2012. Prolonged hyperbilirubinemia was defined as the presence of neonatal jaundice persisting beyond 14 days in term infants, and over 21 days in preterm infants. Collected data of studied neonates were demographic and clinical features, including age, gender, birth weight, gestational age, history of phototherapy, feeding status and history of jaundice in siblings. All the neonates were thoroughly examined by a pediatrician upon admission.

In this study, work-up procedures for infants with prolonged neonatal hyperbilirubinemia were as follows: complete blood count, reticulocyte count, direct Coombs test, blood group evaluation of infants and mothers, blood smear, glucose-6-phosphate dehydrogenase (G6PD) test, assessment of serum bilirubin level (conjugated or unconjugated), thyroid function tests to determine serum concentrations of thyroxine (T4) and thyroid-stimulating hormone (TSH), urinalysis and suprapubic urine culture. Conjugated bilirubin of more than 20% of total bilirubin concentration was considered as abnormal and normal ranges of serum TSH and T4 were 0.5-6 and 8.2-20 mU/L, respectively.

Urine samples were obtained from the neonates via suprapubic aspiration, and UTI was defined as the presence of any colony-forming units (CFU)/ml of pathogens. In addition, breast milk jaundice was diagnosed when the cause of prolonged hyperbilirubinemia was unknown in exclusively breastfed neonates. As such, infants diagnosed with breast milk jaundice were excluded from the study. Moreover, hemolysis was identified in case of low hemoglobin level and high reticulocyte count, along with hemolysis findings on peripheral smears.

Data analysis was performed in SPSS V.16 (SPSS Inc., Il, USA) using Chi-square and Mann-Whitney U tests. Obtained data were presented as mean, standard deviation (SD), frequency and percentage. In addition, studied variables were compared using independent T-test and Chi-square, and $P<0.05$ was considered as significant.

Results

During this study, 100 neonates diagnosed with prolonged jaundice were admitted to the neonatal ward of our hospital, including 49 male and 51 female infants. Mean age of neonates at admission was 20.1±8.2 days, and mean of body weight was 2.99±0.77 kg. Also, mean of serum bilirubin level was estimated at 17.54±4.07 mg/dL, and exclusive breastfeeding was the main method of feeding in the majority of studied patients (71%).

Previous phototherapy was documented in 47% of the infants, and 22% had history of hyperbilirubinemia in their siblings. It is also noteworthy that all male infants enrolled in this study were uncircumcised. Demographic

Table 1. Demographic and General Data of Neonates

Variables	Value
Gender	
Male	49
Female	51
Birth Type	
Full-term Birth	69
Premature Birth	31
Birth Weight (Mean±SD)(Kg)	2.99±0.77
Gestational Age (Mean±SD) (Week)	36.8±2.9
Type of Delivery	
Vaginal	46
Cesarean Section	54
Neonatal Age at Admission (Mean±SD) (Day)	20.1±8.2
Length of Hospital Stay (Mean±SD)(Day)	4.07±2.09
Feeding Method	
Breastfeeding	71
Bottle-feeding	1
Mixed	28
History of Phototherapy for Jaundice	
Yes	47
No	53
History of Phototherapy in Siblings	
Yes	23
No	77
Etiologies	
Breastfeeding	70
Urinary Tract Infection	14
Congenital Hypothyroidism	6
G6PD Deficiency	5
ABO Incompatibility	5
Type of Treatment	
Single Phototherapy	29
Double Phototherapy	19
Intensive Phototherapy	48
Phototherapy and IVIG	1
Phototherapy and Exchange Transfusion	3

*G6PD: Glucose-6-phosphate Dehydrogenase
**IVIG: Intravenous Immune Globulin

characteristics of the studied neonates are presented in Table 1, and laboratory findings are shown in Table 2.

Congenital hypothyroidism, hemolysis (5 cases with G6PD deficiency, 5 cases with ABO incompatibility) and UTI were diagnosed in 6, 10 and 14 neonates, respectively, while the etiology of hyperbilirubinemia was not determined in 70% of the infants; therefore, these cases were considered as breast milk jaundice. Comparison of the neonates in terms of hypothyroidism is presented in Table 3.

Table 2. Serum Laboratory Results of Neonates

Variables	Results
Hemoglobin Level (g/dL)	12.8±2.6
Retic Count (mm^3)	1.3±1.3
Total Bilirubin Level (mg/dL)	17.5±4.0
Conjugated Bilirubin Level (mg/dL)	0.7±0.3
TSH (mU/L)	8.7±3.2
T4 (mU/L)	8.1±3.3

*TSH: Thyroid-stimulating Hormone
**T4: Thyroxine

Table 3. Comparison of Studied Variables in Neonates with and without Congenital Hypothyroidism

Variables	Congenital Hypothyroidism		P-value
	Yes	No	
T4 (mU/L)	3.94±1.37	8.35±3.30	0.004
TSH (mU/L)	19.86±0.85	4.68±4.13	0.000
Hemoglobin (g/dL)	13.4±0.64	12.8±2.7	0.082
Retic Count (mm^3)	1.4±1	1.3±1.4	0.956
Total Bilirubin (mg/dL)	16.9±4.0	17.5±4.0	0.743
Direct Bilirubin (mg/dL)	0.45±0.12	0.80±1.3	0.568
Birth Weight (Kg)	2.66±0.75	2.86±0.60	0.475
Gestational Age (Week)	36.2±5.1	36.8±2.8	0.632
Age at Admission (Day)	17.0±4.5	20.3±8.3	0.213
Gender			
Male	3	46	0.675
Female	2	49	
History of Phototherapy			
Yes	1	46	0.367
No	4	49	

*TSH: Thyroid-stimulating Hormone
**T4: Thyroxine

Table 4. Comparison of Studied Variables in Neonates with and without Urinary Tract Infection (UTI)

Variables	UTI		P-value
	Yes	No	
Hemoglobin (g/dL)	12.4±3.1	12.9±2.6	0.526
Retic Count (mm^3)	0.8±0.4	1.4±1.4	0.150
Total Bilirubin (mg/dL)	14.4±4.2	18.0±3.8	0.002
Direct Bilirubin (mg/dL)	0.6±1.4	0.7±1.2	0.779
Birth Weight (Kg)	3.10±0.43	2.81±0.62	0.101
Gestational Age (Week)	36.5±3.2	36.8±2.9	0.736
Age at Admission (Day)	22.4±12.7	19.8±7.3	0.273
Gender			
Male	10	39	0.088
Female	4	47	
History of Phototherapy			
Yes	8	39	0.565
No	6	47	
Type of Feeding			
Breastfeeding	13	58	0.151
Formula Feeding	0	1	
Both	1	27	

Table 5. Comparison of Studied Variables in Term and Preterm Neonates

Variables	Neonates		P-value
	Term (N=69)	Preterm (N=31)	
Gender			
Male	33	15	0.830
Female	36	16	
Birth Weight (Kg)	3.056±0.497	2.395±0.579	0.000
Weight at Admission (Kg)	3.232±0.624	2.451±0.616	0.000
Gestational Age (Week)	38.4±0.9	33.0±2.4	0.000
Age at Admission (Day)	19.7±8.7	21.1±7.2	0.440
Length of Hospital Stay (Day)	4.0±2.1	4.1±2.0	0.771
Type of Delivery			
Vaginal	34	12	0.389
Cesarean Section	35	19	
Hemoglobin (g/dL)	13.1±2.3	12.1±3.2	0.069
Retic Count (mm^3)	1.1±0.7	1.9±2.1	0.008
Total Bilirubin (mg/dL)	17.4±3.6	17.6±5.0	0.826
Direct Bilirubin (mg/dL)	0.6±1.1	1.0±1.6	0.250
T4 (mU/L)	8.1±3.5	8.0±2.9	0.859
TSH (mU/L)	5.5±4.9	4.4±3.5	0.319
History of Phototherapy			
Yes	27	20	0.019
No	42	11	
Type of Feeding			
Breastfeeding	52	19	0.236
Formula Feeding	1	0	
Both	16	12	
Congenital Hypothyroidism			
Yes	4	1	0.585
No	65	30	
Urinary Tract Infection			
Yes	10	4	0.832
No	59	27	
G6PD			
Sufficient	65	29	0.899
Deficient	4	2	

*TSH: Thyroid-stimulating Hormone
**T4: Thyroxine
***G6PD: Glucose-6-phosphate Dehydrogenase

According to our findings, UTI was more prevalent among male infants. Comparison of other variables in the study population is shown in Table 4. Regarding the isolated microorganisms, *Escherichia coli* was detected in 7 patients, *Klebsiella pneumonia* was observed in 5 cases, *Proteus* was detected in 2 patients, and *Enterobacter cloacae* was observed in one patient. Among our subjects, 31% were premature infants, and history of phototherapy was more frequent in preterm neonates compared to term neonates (Table 5).

Discussion

According to the results of this study, the most common causes of prolonged neonatal jaundice are extended breastfeeding, UTI, hemolysis and congenital hypothyroidism, which is compatible with the findings of previous studies conducted in this regard (2, 8, 13). According to several researches, since no specific etiologies could be confirmed in the majority of infants diagnosed with unconjugated hyperbilirubinemia, breastfeeding is normally reported as the main cause of neonatal jaundice. In the present study, breast milk jaundice was identified in 70% of neonates, while in other studies, 53-92% of neonates have been reported to be diagnosed with breast milk jaundice (2, 8, 13).

In the current study, UTI was detected in 14% of the infants, while in other studies, only 5.8-8% of neonates were diagnosed with UTI (8-9, 14, 15). In this regard, frequent UTI pathogens were *Escherichia coli* (7 patients), *Klebsiella pneumoniae*

(5 patients), *Proteus* (2 patients) and *Enterobacter cloacae* (one patient). Furthermore, E. coli was observed to be the most common organism in patients with UTI, and there was no significant difference between the infants in terms of gender, gestational age, birth weight, age at admission and total bilirubin level. This finding is correspondent with the results obtained by Khaleesi et al. and Chen TH et al. (16, 17), while inconsistent with the findings of Hang Ta Chen et al., who reported of a significantly lower hemoglobin level and higher formula feeding rate in infants diagnosed with UTI compared to those without UTI. In this regard, we found no significant difference between these two groups; therefore, UTI was considered as a major cause of prolonged jaundice. It is recommended that urine cultures be obtained from all the infants diagnosed with prolonged hyperbilirubinemia.

Congenital hypothyroidism largely contributes to the development of prolonged jaundice in neonates, and its prevalence was estimated at 1-6.3% in the current study (10-12). Moreover, hypothyroidism was detected in six neonates (total: 100), and this finding was compatible with the results obtained by previous studies (12, 18). In the current study, hypothyroidism was the third most frequent cause of prolonged jaundice in neonates, and no significant difference was observed in this regard between infants with and without congenital hypothyroidism.

In the present study, G6PD deficiency was identified in 5% of patients, which was comparatively lower than the rate reported by Abdel-Fattah et al. (14.4%) and higher than the estimated rate of 2.1% by Abolghasemi et al. (19, 20). In another study, Ahmadi et al. reported the frequency of G6PD deficiency to be 13.6% among neonates, and most of the cases were non-hemolytic (21). According to several researches, G6PD deficiency is a major contributing factor associated with prolonged neonatal jaundice; therefore, it is recommended that newborns be screened for G6PD deficiency on a regular basis.

In the present study, ABO incompatibility was detected in 5% of the neonates, which is consistent with the findings of previous studies in this regard (9, 15). It should also be noted that prematurity directly contributes to the development of neonatal hyperbilirubinemia, and 31% of the infants in our study were premature. In another study, it was stated that premature infants who were breastfed had higher peak bilirubin plasma concentration, and consequently, were more commonly presented with prolonged hyperbilirubinemia compared to neonates using formula feeding (22).

Conclusion

According to the results of this study, although breastfeeding is considered as a major cause of prolonged neonatal jaundice, identification of other pathological factors, such as UTI, congenital hypothyroidism, Crigler-Najjar syndrome and hemolysis is also of paramount importance. Early diagnosis and treatment of these disorders could effectively prevent further complications in neonates.

Acknowledgments

We would like to thank all collogues who participated in this study.

References

1. Mackinlay GA. Jaundice persisting beyond 14 days after birth. BMJ. 1993; 306(6890):1426-7.
2. Hannam S, McDonnell M, Rennie JM. Investigation of prolonged neonatal jaundice. Acta Paediatr. 2000; 89(6):694-7.
3. Schneider AP. Breast milk jaundice in the newborn: A real entity. JAMA. 1986; 255(23):3270–4.
4. Hargreaves T. Breast-milk jaundice. BMJ. 1970; 3(5723):647.
5. Alonso EM, Whitington PF, Whitington SH, Rivard WA, Given G. Enterohepatic circulation of nonconjugated bilirubin in rats fed with human milk. J Pediatr. 1991; 118(3):425-30.
6. Garcia FJ, Nager AL. Jaundice as an early diagnostic sign of urinary tract infection in infancy. Pediatrics. 2002; 109(5):846-51.
7. Jafarzadeh M, Mohammadzadeh A. Should urine culture be considered in the hyperbilirubinemia workup of neonate. J Chinese Clin Med. 2009; 4(3):136-8.
8. Najati N, Gharehbaghi MM, Mortazavi F. Underlying etiologies of prolonged icterus in neonates. Pak J Biol Sci. 2010; 13(14):711-4.
9. Pashapour N, Nikibakhsh AA, Golmohammadlou S. Urinary tract infection in term neonates with prolonged jaundice. Urol J. 2007; 4(2):91-4.
10. Kurtoğlu S, Çoban D, Akın MA, Akın L, Yıkılmaz A. Neonatal sludge: A finding of congenital hypothyroidism. J Clin Res Pediatr Endocrinol. 2009; 1(4):197–200.
11. Araz NC. Frequency of congenital hypothyroidism in the newborns with prolonged jaundice. Gaziantep tip Dergisi. 2009; 15(1):28-30. (Turkish)
12. Honarpisheh A. Frequency of congenital hypothyroidism among neonates with prolonged

jaundice in Kashan. Teb Va Tazkieh. 2004; (51):33-6.
13. Unal S, Aktas A, Ergenekon E, Koc E, Atalay Y. Prolonged jaundice in newborns: What is it actually due to? Gazi Med J. 2003; 14(4):147-51.
14. Bilgen H, Ozek E, Unver T, Biyikli N, Alpay H, Cebeci D. Urinary tract infection and hyperbilirubinemia. Turk J Pediatr. 2006; 48(1): 51-5. (Turkish)
15. Ghaemi S, Fesharaki RJ, Kelishadi R. Late onset jaundice and urinary tract infection in neonates. Indian J Pediatr. 2007; 74(2):139-41.
16. Khalesi N, Sharaki T, Haghighe M. Prevalence of urinary tract infection in neonates with prolonged jaundice. J Qazvin Univ Med Sci. 2007; 11(3):14-8.
17. Chen HT, Jeng MJ, Soong WJ, Yang CF, Tsao PC, Lee YS, et al. Hyperbilirubinemia with urinary tract infection in infants younger than eight weeks old. J Chin Med Assoc. 2010; 74(4):159-63.
18. Scott R, Aladangady N, Maalouf E. Neonatal hypopituitarism presenting with poor feeding, hypoglycemia and prolonged unconjugated hyperbilirubinemia. J Matern Fetal Neonatal Med. 2004; 16(2):131-3.
19. Abdel Fattah M, Abdel Ghany E, Adel A, Mosallam D, Kamal S. Glucose-6-phosphate dehydrogenase and red cell pyruvate kinase deficiency in neonatal jaundice cases in Egypt. Pediatr Hematol Oncol. 2010; 27(4):262-71.
20. Abolghasemi H, Mehrani H, Amid A. An update on the prevalence of glucose-6-phosphate dehydrogenase deficiency and neonatal jaundice in Tehran neonates. Clin Biochem. 2004; 37(3):241-4.
21. Ahmadi AH, Ghazizadeh Z. Evaluation of glucose-6-phosphate dehydrogenase deficiency without hemolysis in icteric newborns at Mazandaran province, Iran. Pak J Biol Sci. 2008; 11(10):1394-7.
22. Kamal S, Sayedda K, Shahir Ahmed Q. Breast non feeding: Main cause of neonatal hyperbilirubinemia in areas adjoining Shri Ram Murti smarak institute of medical sciences, a tertiary care teaching hospital, Bareilly. Natl J Physiol Pharm Pharmacol. 2012; 2(2):108-12.