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Fallah R, Karimi M, Barzegar Bafrooee H. Does moderate unconjugated hyperbilirubinemia in healthy term neonates play a role on their neurodevelopmental status at the age of 18 months? J Med Liban 2013 ; 61 (3) : 170-174.

ABSTRACT • AIM : Safety of moderate hyperbilirubinemia in healthy term neonates is still a matter of discussion. The purpose of this study was to compare developmental status of 18-month-old children with and without history of neonatal indirect non-hemolytic hyperbilirubinemia.

METHODS : In a case-control study, the developmental status of 18-month-old children referred to Azadshar primary health care center in Yazd, Iran, between December 2007 and June 2009 was evaluated via the Persian version of Ages and Stages Questionnaires (ASQ).

Children in the case group were healthy term neonates with total serum bilirubin level of 20-25 mg/dl, birth weight of 2500-4000 g and no birth asphyxia who were admitted to hospital and had undergone phototherapy.

The control group consisted of children who were healthy term neonates without history of neonatal hyperbilirubinemia.

RESULTS : 112 children (56 in each group) were evaluated. Four children in the case group and one in the control group had delay in communication skills. Three in the case group and three in the control group had fine motor delay. Only one child in the case group showed delay in problem solving.

Statistically significant differences were not seen in the frequency of developmental delay as well as in the mean scores of all developmental domains in both groups.

CONCLUSION : Based on the results of the present study by ASQ, the developmental status at the age of 18 months of healthy term neonates with moderate unconjugated hyperbilirubinemia was not different from the control group.

Keywords : hyperbilirubinemia, neonate, child development, Ages and Stages Questionnaires (ASQ)

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Fallah R, Karimi M, Barzegar Bafrooee H. L'hyperbilirubinémie modérée non conjuguée chez des nouveau-nés à terme et en bonne santé cause-t-elle des retards de développement à l'âge de 18 mois? J Med Liban 2013 ; 61 (3) : 170-174.

RÉSUMÉ : OBJECTIF : L'innocuité de l'hyperbilirubinémie modérée chez des enfants nés à terme et en bonne santé est controversée. Le but de cette étude est de comparer le développement d'enfants âgés de 18 mois avec et sans antécédent d'hyperbilirubinémie néonatale indirecte et non hémolytique.

MÉTHODES : Dans une étude cas-témoin, le développement des enfants de 18 mois référés au centre de soins primaires d'Azadshar (Yazd, Iran), entre décembre 2007 et juin 2009, a été évalué à l'aide de la version en persan des questionnaires ASQ (*Ages and Stages Questionnaires*). Les enfants du groupe de cas étaient nés à terme avec un score d'Appgar de 8-10, un poids de naissance de 2500-4000 g, une bilirubine sérique totale de 20-25 mg/dl; admis à l'hôpital, ils avaient été traités par photothérapie. Le groupe témoin comprenait les enfants nés à terme et en bonne santé, sans hyperbilirubinémie néonatale.

RÉSULTATS : 112 enfants (56 dans chaque groupe) ont été évalués. Dans le domaine de la communication, quatre enfants du groupe de cas et un du groupe témoin avaient du retard. Trois du groupe de cas et trois du groupe témoin présentaient un retard en motricité fine. Un seul enfant du groupe de cas a montré un retard à résoudre des problèmes. Des différences statistiquement significatives n'ont pas été retrouvées dans la fréquence des retards de développement ainsi que dans les scores moyens de tous les domaines de développement dans les deux groupes

CONCLUSION : Sur base des résultats de la présente étude ASQ, l'hyperbilirubinémie non conjuguée chez des nouveau-nés à terme et en bonne santé ne cause pas de retard de développement à l'âge de 18 mois.

Mots-clés : hyperbilirubinémie, nouveau-né, développement de l'enfant, ASQ (Age-Stage-Questionnaire)

INTRODUCTION

In neonates, unconjugated bilirubin in toxic level crosses the blood brain barrier and accumulates in the basal ganglia and brainstem nucleus causing acute and chronic bilirubin encephalopathy (classical kernicterus) or subtle neurodevelopmental disabilities. Regardless of etiology, appropriate intervention should be considered in severe

hyperbilirubinemia to prevent bilirubin neurotoxicity [1].

Kernicterus is rare in healthy term and in late preterm neonates with total serum bilirubin (TSB) level of less than 25 mg/dl [2]. But, safety of moderate hyperbilirubinemia in healthy term neonates is still a matter of discussion. In some studies, neonatal jaundice was associated with increased risk of subsequent psychological development disorders, infantile autism [3], attention-deficit disorder [4] and neurological and developmental sequel [5]. However, in some other studies, neurodevelopmental outcome of healthy term newborns with moderately severe non-hemolytic hyperbilirubinemia and infants with less severe or no hyperbilirubinemia, was not different [4, 6-7].

Assessment of children by different developmental screening tests may be done by trained professionals or by their parents. Parental reports screening tests, one of which is Ages and Stages Questionnaires (ASQ), are cost-effective, easy to complete, time saving and eliminate challenges of extracting skills from children who, by reasons such as illness, sleepiness, anxiety and fear, may not do their best on the testing day which may lead to true problems not being detected. A failed developmental screening test indicates the need for further diagnostic assessment and more comprehensive evaluation [8].

ASQ is one of parental reports screening tests: its sensitivity varies between 87% and 100%, its specificity for detection of severe developmental delay is 82-93% depending on the evaluation age. ASQ gold standard and validity is 76-88% [8-9].

The purpose of this study was to evaluate and compare the developmental status at 18 months of age of healthy term neonates with total serum bilirubin level of 20-25 mg/dl with those without neonatal hyperbilirubinemia via the Persian version of the ASQ test in Yazd, central city of I.R. Iran.

METHODS

According to vaccination programs in Iran, 18-month-old children should be routinely referred to preventive health care centers. In a case-control study by sample size – based on Z formula and confidence interval of 95% with 80% power to detect a 20% difference in frequency of developmental delay between groups with type one error (α) of 0.05 and beta (β) set at 0.2 – a total of 112 children, 56 per group, were assessed, and the developmental status of 18-month-old children referred for vaccination to Azadshar primary health care center in Yazd, Iran, between December 2007 and June 2009, was evaluated.

The Azadshar center is one of several primary health care facilities located in Yazd, central city of Iran, and the socioeconomic status of families who live in this area is the same.

At first, a research pediatric neurologist interviewed and explained to the mothers the importance of developmental evaluation and early detection of developmental disabilities and they were asked to take part in the study.

Upon their agreement, an informed consent was obtained and their children enrolled in the study until sample size was completed.

Based on information from the health care center records, the children were distributed into two groups. Children with a history of neonatal hyperbilirubinemia who were admitted to hospital, were selected as case group, and children in control group were healthy term neonates without a history of neonatal hyperbilirubinemia nor neonatal admission. All children in case and control groups had exclusive breast feeding for the first six months of age.

Then the medical records of neonates with hyperbilirubinemia were evaluated and care was taken to include healthy term neonates who :

1. had a gestational age of 37-42 weeks;
2. had a birth weight of 2500-4000 g;
3. were without birth asphyxia and hypoxic ischemic insults;
4. had a total serum bilirubin level of 20-25 mg/dl;
5. were discharged in good general condition and TSB level of less than 10 mg/dl during the first ten days of their lives.

Multiple pregnancies, preterm neonates (gestational age less than 37 weeks), small for gestational age (SGA), pathologic jaundice (hemolytic anemia, jaundice in first 24 hours, kernicterus and exchange transfusion, sepsis, direct hyperbilirubinemia and hepatic diseases), severe asphyxia, hypothyroidism, prolonged hyperbilirubinemia (jaundice present at or beyond age 3 weeks) and children with major congenital malformations, chromosomal abnormalities and genetic syndromes, were excluded.

The developmental status of the children was assessed after interview with their parents by the Persian version of the 60-month ASQ screening test in all cases and controls.

This test includes 19 different questionnaires that can screen developmental status of the children from four to 60 months in five different domains: communication, gross motor, fine motor, problem solving and personal social skills through six questions per domain regarding what the child can or cannot do. The answer of parents to each question is “yes” to indicate that the child does the specific behavior of this item, “sometimes” to indicate an occasional or emerging response, and “not yet” to indicate that their child has not yet acquired the skill, with a respective score of 10, 5 or 0 points. Then scores of each item are summed up and the final score in each domain is compared to cut-off points of the ASQ guidelines. Any score below the cut-off point or higher than two standard deviations below the mean of the reference group, is considered abnormal and implies a referral for further evaluation [8-9].

The questionnaire was completed by the research general physician, unaware of the subjects' study-group status, who asked the questions to the mothers.

The data were analyzed using SPSS:15 statistical software. Chi-square test or Fisher exact test were used for data analysis of qualitative variables and mean values

TABLE I COMPARISON of MOTHER AGE and BIRTH WEIGHT in the TWO GROUPS			
DATA	Hyperbilirubinemia		p value
	Group with Mean ± SD	Group without Mean ± SD	
Mother age (y)	24.35 ± 3.2	24.82 ± 4.16	0.81
Birth weight (g)	2951.39 ± 100.97	3072.22 ± 97.55	0.65

were compared using independent T-test. Differences were considered significant at p value < 0.05.

This study was approved by the ethic committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

RESULTS

A total of 112 children including 58 girls (51.8%) and 54 boys (48.2%) were evaluated.

Thirty-three children (59%) in the case group and 25 (44.7%) in the control group were female and sex distribution was not different in both groups (p value = 0.13).

Route of delivery was cesarean section in 32% (N = 18) and 35.7% (N = 20) in case and control groups respectively and cesarean rate was not different in both groups (p value = 0.9).

Table I shows comparison of mean mother age and mean birth weight in both groups and indicates that there were no statistically significant differences from these view points in both groups.

In the hyperbilirubinemic group, mean age of neonates while admitted to hospital was 7.8 ± 1.2 days and mean of maximum TSB during admission period was $22.8 \pm$

TABLE II FREQUENCY of DEVELOPMENTAL DELAY in EACH DEVELOPMENTAL DOMAIN in BOTH GROUPS			
DEVELOPMENTAL DOMAIN	Hyperbilirubinemia		p value
	Group with	Group without	
GROSS MOTOR			
Normal	56	56	0
Delay	0	0	
FINE MOTOR			
Normal	53	53	1
Delay	3	3	
PROBLEM SOLVING			
Normal	55	56	0.99
Delay	1	0	
PERSONAL SOCIAL			
Normal	56	56	0
Delay	0	0	
COMMUNICATION			
Normal	52	55	0.364
Delay	4	1	

2.4 mg/dl. All hyperbilirubinemic neonates were discharged when TSB was achieved to less than 10 mg/dl. Etiology of jaundice and duration of icterus was not assessed in this study, but pathologic and prolonged jaundices were excluded, and only healthy term neonates were included.

Frequency distribution of developmental delay in all developmental domains of both groups is shown in Table II: 5.3% (N = 6) of all children (three children in each group) had fine motor delay; 4.5% (N = 5) of all children (four in case group and one child in control group) had delay in communication domain; 0.9% of all children (only one child in case group) showed delay in problem solving domain and 14.3% (N = 8) of children with moderate neonatal hyperbilirubinemia had delay in developmental domains, but statistically significant differences were not seen in frequency of delay in all developmental domains in both groups.

Comparison of mean scores in all developmental domains is presented in Table III which indicates that the better assessed score in case and control groups was in gross motor domain and that the lesser assessed score in case and control groups was in communication domain. But independent T-test showed that statistically significant differences were not seen in mean score of all developmental domains in case and control groups.

DISCUSSION

Based on the results of the present study using ASQ questionnaire, developmental status at the age of 18 months of healthy term neonates with unconjugated hyperbilirubinemia at 20-25 mg/dl level who were treated with phototherapy alone, was not different from the control group. Our findings are in agreement with other studies [4, 6, 10-14] some of which, however, evaluated different cases : • children aged between 1 and 5 years with severe neonatal hyperbilirubinemia (at least one measure of TSB \geq 25 mg/dl during the first three weeks of life) in Vandborg *et al.* [10], based on the parent-completed ASQ • two-year-olds with TSB level of 25-30 mg/dl in Newman *et al.* [11] • three-year-old children with TSB level of 20-30 mg/dl in Heimler *et al.* [6], using Bailey test

TABLE III COMPARISON of MEAN SCORES in ALL DEVELOPMENTAL DOMAINS in the TWO GROUPS			
DEVELOPMENTAL DOMAIN	Hyperbilirubinemia		p value
	Group with Mean ± SD	Group without Mean ± SD	
Gross motor	58.57 ± 3.12	57.85 ± 3.79	0.376
Fine motor	51.53 ± 7.27	50.98 ± 7.94	0.718
Problem solving	51.9 ± 8.68	51.81 ± 5.49	0.333
Personal-social	55.53 ± 4.54	55.17 ± 5.95	0.773
Communication	50.85 ± 10.79	50.14 ± 8.09	0.376

- healthy term and late preterm infants with TSB levels ≥ 19 mg/dl in a 2-9 year follow-up period in Jangaard *et al.* in Canada [4]
- three-year-olds with TSB level of 17.5-30 mg/dl in Wong *et al.* [12]
- five-year-old children with TSB levels ≥ 30 mg/dl in Newman *et al.* [13]
- three-year-olds with severe hemolytic hyperbilirubinemia in Chen *et al.* [14].

Our results differ from findings of researchers such as Oh *et al.* who reported that in extremely low birth weight infants, an increasing level of unbound bilirubin is associated with a higher risk of neurodevelopmental delay in unstable, but not in stable ones [15]; Gordon *et al.* in Kenya, who found an increased prevalence of neurodevelopmental delay in infants with TSB of 17 mg/dl [5]; Arimbawa *et al.* in Indonesia who reported increased risk of gross motor delay in hyperbilirubinemic infants at the age of six months [16]; Soorani-Luning *et al.* who found a significant increase in minor neurologic dysfunction at the ages of 3 and 12 months of 20 healthy term newborns with TSB levels of 13.6-26.4 mg/dl [17]; and Arun Babu *et al.* in India who concluded that peak serum bilirubin ≥ 22 mg/dl, Rh incompatibility and occurrence of jaundice within two days of life is associated with increased incidence of abnormal developmental quotient at the age of 6 months [18].

Possible explanations for these discrepancies are differences in sample size, selection method of patients, geographic area, race, methods of sample selection and level of TSB and etiology of jaundice.

In the present study, via ASQ, 14.3% (N = 8) of children with moderate neonatal hyperbilirubinemia, had delay in developmental domains. Also, in Wolf *et al.* study in Zimbabwe, 11% of five-year-old children with TSB > 23.4 mg/dl scored abnormal on the Bayley Scales of Infant Development test [19].

Development is concerned with a dynamic and progressive process and early developmental assessment should be routinely and regularly done before school entrance for early and timely diagnosis, investigation, management and rehabilitation.

In this study, developmental status was assessed via ASQ test by the parents. In another Iranian study, this test was used to evaluate the developmental status of moderately low birth weight (MLBW: birth weight 1500-2499 g) children at the age of five years; the frequency of developmental delays in gross motor, fine motor and problem solving domains were significantly higher in the MLBW group [20].

It should be mentioned that ASQ is one of developmental screening tests and not a diagnostic one. It should also be interpreted as a whole rather than by developmental domains and its results are not absolute, its capacity to identify those with milder delay is limited [21]. In this test, children with scores below the cut-off point or higher than two standard deviations below the mean of the reference group on any domain must be referred for further evaluation by diagnostic tests and investigations.

There are several limitations to this study. First, its small

sample size. Second, some infants might have had hyperbilirubinemia that was unrecognized and did not lead to investigation and admission. Such infants would have been misclassified as "without hyperbilirubinemia." Third, some disorders (such as attention deficit disorder, autism spectrum disorder and mild mental retardation) are typically diagnosed after two years of age. Therefore, it is suggested that further studies be conducted with larger sample sizes, longer follow-up periods, using other developmental screening tests such as Denver II, the Bayley Neurodevelopmental screener, the Batelle Developmental Inventory, etc., and comparing this developmental screening test with diagnostic developmental delay tests.

In conclusion, based on the results of the present study using ASQ developmental screening test, the developmental status at 18 months of age of healthy term neonates with unconjugated 20-25 mg/dl hyperbilirubinemia, was not different from that of the control group.

ACKNOWLEDGMENTS

We thank the Deputy for Research of Shahid Sadoughi University of Medical Sciences, Yazd, Iran, for his support. We also thank the health workers community of Azadshar Primary Health Care Center for facilitating our access to the data.

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