Follow-up of Neonates With Total Serum Bilirubin Levels ≥25 mg/dL: A Danish Population-Based Study

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KEY WORDS
neonates, hyperbilirubinemia, follow-up, Ages and Stages Questionnaire, development

ABBREVIATIONS
ASQ—Ages and Stages Questionnaire
CI—confidence interval
TSB—total serum bilirubin

Drs Vandborg, Ebbesen, Moelholm Hansen, and Greisen planned the study; Drs Vandborg and Jepsen collected the data; Dr Moelholm Hansen extracted and analyzed data from Statistics Denmark; Dr Vandborg performed the statistical analysis and drafted the primary article; all authors participated in analysis and interpretation of data; and all authors contributed to the final manuscript.

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WHAT'S KNOWN ABOUT THIS SUBJECT: Neonatal hyperbilirubinemia may progress to bilirubin encephalopathy. Findings from previous studies on long-term development of neonatal hyperbilirubinemia are conflicting.

WHAT THIS STUDY ADDS: Using Ages and Stages Questionnaire, we observed no association between bilirubin exposure and overall development in 1- to 5-year-old children who in the neonatal period had total serum bilirubin level ≥25 mg/dL and no or only minor neurologic symptoms.

abstract

OBJECTIVE: To study if severe hyperbilirubinemia in infants with no or minor neurologic symptoms in the neonatal period affects children's development at the age of 1 to 5 years.

METHODS: Controlled descriptive follow-up study of a national cohort of Danish children. The exposed group consisted of all live-born infants in Denmark from 2004 to 2007 with a gestational age ≥35 weeks and severe hyperbilirubinemia in the neonatal period, defined as at least 1 measure of total serum bilirubin level ≥25 mg/dL during the first 3 weeks of life. The exposed group of 206 children was matched with a control group of 208 children. The Ages and Stages Questionnaire (ASQ), a method of evaluating the child's development, was filled in by parents. Main outcome measure was effect size of ASQ total score. Statistical analyses comprised a matched analysis of 102 pairs and a nonmatched regression analysis of all participants.

RESULTS: The response rate was 79% (n = 162 of 206) in the study group and 70% (n = 146 of 208) in the control group. Neither the matched nor the nonmatched analysis showed any statistically significant differences between the groups; the effect size of the total score was 0.04 (−0.24 to 0.32) and −0.04 (−0.26 to 0.19), respectively.

CONCLUSIONS: Using the parent-completed ASQ, we found no evidence of developmental delay in children aged between 1 and 5 years with severe neonatal hyperbilirubinemia compared with a matched control group. *Pediatrics* 2012;130:61–66

Jaundice caused by unconjugated hyperbilirubinemia is seen in most newborn infants during the period of the infant's adaptation to extrauterine life. It is usually a benign condition that resolves spontaneously. Occasionally, the serum bilirubin concentration rises to severe and even extreme levels and may cause acute and chronic bilirubin encephalopathy. The reported incidence of severe hyperbilirubinemia in term and late preterm infants in the industrialized countries has been constant over the past 20 years.[1–5]

Acute bilirubin encephalopathy can be divided into 3 phases: early, intermediate, and advanced. The early phase is characterized by lethargy, hypotonia, and decreased feeding; the intermediate phase is characterized by alternating tonus, irritability, high-pitched cry, retrocollis, and opistotonus; and the advanced phase is characterized by sun setting sign, seizures, coma, and eventually, death.[6]

It is well described that term and late preterm infants with severe or extreme hyperbilirubinemia presenting with intermediate or advanced acute bilirubin encephalopathy in the neonatal period may develop chronic sequelae[7,8]; however, it remains controversial whether infants with severe or extreme hyperbilirubinemia presenting with minor or no neurologic symptoms in the neonatal period may develop more subtle brain injury, causing developmental problems.[3,4,9–18] The aim of this study was to assess the developmental status of term and late preterm infants with severe and extreme neonatal hyperbilirubinemia (total serum bilirubin [TSB] level ≥25 mg/dL [note: 1 mg/dL = 17 μmol/L]) with no symptoms of intermediate or advanced bilirubin encephalopathy in the neonatal period compared with a matched control group.

METHODS

This Danish national cohort study included data on all 250 047 live-born infants in the study period from January 1, 2004 to December 31, 2007. In Denmark, all citizens are assigned a civil registration number at birth. By using the civil registration number, data can be linked across registries and databases. The system ensures complete data for research purposes.

The exposed group consisted of all live-born infants with a gestational age ≥35 weeks and severe hyperbilirubinemia in the neonatal period, defined as at least 1 measure of TSB level ≥25 mg/dL during the first 21 days of life. The group was identified by electronically stored laboratory data, and medical records were retrieved by using the civil registration number. Data from the neonatal period on symptoms of encephalopathy were collected. Infants with intermediate or advanced acute bilirubin encephalopathy, rhesus isoimmunization, and conjugated hyperbilirubinemia were excluded. A control group of children matched 1:1 to the exposed group on gender, age (±30 days), gestational age (±10 days), and municipality of residence was identified in the Danish Birth Registry.

We obtained data from Statistics Denmark on the entire cohort to adjust for selection bias. We extracted data from the National Registry of Education on the level of maternal education and ethnicity and from the Danish National Patient Registry on neurologic diagnoses from second-level health care (International Classification of Diseases, 10th Revision codes G80-83 and G40). The families of the children in both groups were mailed the Ages and Stages Questionnaire (ASQ) and another questionnaire on parents' educational level and ethnic origin. If a family did not return the questionnaires within 2 weeks, a reminder was sent. The family was contacted by telephone if the questionnaires were not returned within a month. The educational level of the mother was used as an indicator of social class and categorized into 3 groups: (1) primary school, (2) high school/college, and (3) university education.[19]

ASQ

The ASQ is a system of parent-completed questionnaires evaluating development in children aged from 6 months to 5 years. It consists of 19 different questionnaires covering the ages of 4 months to 60 months. In this study, we used only 5 questionnaires (18, 24, 33, 48, and 60 months of age). The ASQ has been validated and compared with Griffith Mental Development Scale, Bayley Mental Development Intelligence Scale, and McCarthy General Cognitive Intelligence Scale.[20] In 2004, it was translated into Danish and validated and compared with Wechsler Preschool and Primary Scale of Intelligence-Revised by Klamer et al[21] with a fairly good result. The questionnaires are completed by the parents based on their knowledge about their child's development and after performing certain tasks with the child. It takes ~30 to 60 minutes to complete.

Each of the 19 questionnaires consists of 6 questions within 5 different domains: communication, gross motor skills, fine motor skills, problem solving, and personal-social skills. Each question can be answered "yes" (10 points), "sometimes" (5 points), or "no" (0 points). The total raw score ranges from 0 to 300 points. When the ASQ is used as a screening program, children performing better than average score near the maximum, resulting in an underestimation of the mean. To provide a normal distribution of the ASQ raw score, the families were mailed a questionnaire meant for children who were 6 months older.

Ethics

The study was approved by the Danish Data Protection Agency and the Central Denmark Region Committees on Biomedical Research Ethics.

Statistical Analyses

To estimate the difference in ASQ total scores between the exposed and the control group, 2 main analyses were made: a matched analysis based on the study design and a nonmatched analysis including all participants. Effect size for each domain and the total score was calculated from the adjusted difference in raw score between the groups divided by the common reference population ASQ SD. The calculation of the common SD was made by using a multiple linear regression analysis with group (exposed/nonexposed) and ASQ questionnaire number as the categorical variable and adjusted age (ie, age at the time the questionnaire was filled in corrected for preterm birth until gestational age of 40 weeks) as the continuous variable, allowing for interaction between age and questionnaire number.

Matched Analysis

The difference in raw score between the groups was calculated by using a paired *t* test. Based on the paired study design, the raw score was automatically adjusted for age, gestational age, gender, and municipality of residence.

Nonmatched Analysis

The difference in raw score was estimated by using multiple linear regression analysis adjusting for ASQ questionnaire number, gestational age (35–37 weeks/38–42 weeks), gender, adjusted age, parental educational score (primary school, high school/college, university education), and ethnicity (Caucasian/non-Caucasian).

In both the matched and the nonmatched analysis, we used the previously mentioned SD as the reference population ASQ SD. A comparison between participants and nonparticipants was made with regard to peak TSB level (only the exposed group), gender, and gestational age by using a nonpaired *t* test. The level of maternal education and ethnicity was compared by χ^2 analysis by using data from the National Registry of Education. Using χ^2 analyses, we also compared the number of children with a neurologic diagnosis in the entire exposed group with the entire control group. The statistical significance level was 5%. Data were analyzed by using Stata software version 11 (Stata Corp, College Station, TX).

RESULTS

During the study period, 258 infants with gestational age ≥35 weeks with a TSB level ≥25 mg/dL were identified; this is equivalent to an incidence of 103 per 100 000 newborns. A flowchart of the study cohort is shown in Fig 1. Owing to the strict match criteria, it was not possible to precisely match the groups 1:1, so 232 exposed infants were matched with a control group of 224 infants. Based on data retrieved from the medical records, 5 infants in the exposed group were excluded: 2 children had intermediate or advanced acute bilirubin encephalopathy; 1 child had conjugated hyperbilirubinemia; 1 child had a gestational age <35 weeks (a registration error in the Danish Birth Registry); and 1 child had rhesus isoimmunization. The questionnaires were mailed to the families of 206 exposed and 208 nonexposed children. The overall response rate was 74%: 79% (*n* = 162 of 206) in the exposed group and 70% (*n* = 146 of 208) in the nonexposed group.

Demographic and clinical data of all participating infants are shown in Table 1. The median peak TSB level was 26 mg/dL, and median time of the peak TSB level was 4 days. At time of phototherapy, 89 of the infants (55%) had early acute bilirubin encephalopathy, and all but 1 received phototherapy (*n* = 161). The infant who did not recieve phototherapy was not referred to the hospital by the general practitioner.

The main results of the ASQ are presented in 2 analyses: a matched analysis (Table 2) and a nonmatched analysis (Table 3). The matched analysis is based on pairs of 102 infants in each group. The mean ASQ total raw score ±SD was 224.71 ± 43.84 for the exposed group and 223.19 ± 43.90 for

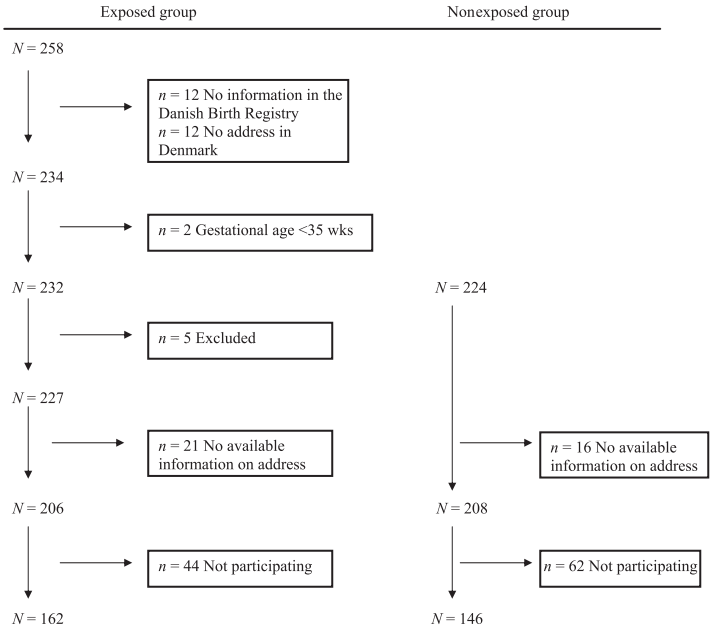

FIGURE 1
Flowchart of exposed and nonexposed groups.

TABLE 1 Clinical and Demographic Data for the Exposed and the Nonexposed Group

	Exposed Group, *n* = 162	Nonexposed Group, *n* = 146
Gestational age, wk; median (range)	38.5 (35.0–42.7)	38.7 (35.7–42.1)
Birth weight, g; median (range)	3470 (2550–4640)	3356 (1930–4680)
Gender, *n* (%)		
Female	77 (48)	65 (45)
Male	85 (52)	81 (55)
Apgar score ≤7 at 5 min, *n* (%)	1 (0.5)	0 (0)
Ethnicity, *n* (%)		
Caucasian	142 (88)	135 (92)[a]
Non-Caucasian	20 (12)	9 (6)
Parental education groups, *n* (%)[b]		
Primary school	57 (35)	55 (38)
High school/college	55 (34)	43 (29)
University education	48 (30)	46 (32)
TSB peak, mg/dL; median (range)	26 (25–35)	
TSB peak, d; median (range)	4 (1–17)	
Early acute bilirubin encephalopathy, *n* (%)	89 (55)	

[a] Information on ethnicity from questionnaire was missing for 2 children.

[b] Information on parental education group was missing for 2 exposed and 2 nonexposed children.

the nonexposed group. There were no statistically significant differences between the groups in the total score or in any of the 5 domains. The effect size of the total score was 0.04, mean (95% confidence interval [CI]: −0.24 to 0.32). Similarly, the nonmatched analyses showed no statistically significant differences in the total score and in the score of the 5 domains between the exposed and the nonexposed group. The effect size of the total score was −0.04, mean (95% CI: −0.26 to 0.19).

The data of the nonmatched analysis were stratified into 5 different age groups (18, 24, 33, 48, and 60 months). No statistically significant differences were observed between exposed and nonexposed children in total score or in the 5 domains (data not shown). The results of the multiple regression analysis on potential confounders of the effect size of the total ASQ score are shown in Table 4. Boys had statistically significantly lower scores than girls ($P < .001$), and children of parents with a high educational level had statistically significantly higher scores compared with children of parents with no or short educations ($P = .04$). When comparing participants and nonparticipants within both groups regarding TSB level (only the exposed group), gender, gestational age, maternal educational level, and ethnicity, no statistically significant differences were found. Median peak TSB levels were 26 mg/dL (95% CI: 25.8–26.5) for participants and 26.5 mg/dL (95% CI: 26–27) for nonparticipants.

By using data from the Danish National Patient Registry on neurologic diagnoses, we found 1 child with a nervous system disorder and 1 child with epilepsy in the exposed group ($n = 227$) compared with no children with these diagnoses in the nonexposed group ($n = 224$) ($P = .35$ and $P = .35$, respectively, when comparing the two groups). The 2 children with a neurologic diagnosis both participated in the study.

DISCUSSION

The objective of this study was to demonstrate possible developmental adverse effects of severe and extreme neonatal hyperbilirubinemia in a Danish national cohort of children between 1 and 5 years of age with a gestational age ≥35 weeks and a peak TSB level ≥25 mg/dL; the children had either no neurologic symptoms or only early acute bilirubin encephalopathy in the neonatal period. An effect on general psychomotor development could be taken as an indication of subtle brain damage caused by asymptomatic hyperbilirubinemia and could have wide implications for neonatal practice and for the practice of litigation and compensation. We evaluated general development by using the total ASQ score, and we found no evidence of a general effect on the development in children exposed to severe and extreme bilirubin levels in comparison with a control group. There were no signs of more specific developmental problems when comparing the ASQ scores in the 2 groups in the 5 different domains: communication, gross motor skills, fine motor skills, problem solving, and personal-social skills.

Our results are in accordance with most previous studies investigating the long-term complications of hyperbilirubinemia regarding development, IQ,

TABLE 2 ASQ Scores for the Exposed and Nonexposed Groups: Matched Analysis

	Exposed Group, *n* =102	Nonexposed Group, *n* =102	Difference		
	Raw Score, Mean ± SD	Raw Score, Mean ± SD	Raw Score, Mean (95% CI)	Effect Size, Mean (95% CI)	*P*
Communication	42.54 ± 14.64	41.48 ± 15.84	1.06 (−2.42 to 4.54)	0.09 (−0.20 to 0.37)	.55
Gross motor	48.14 ± 10.28	47.77 ± 10.87	0.49 (−2.11 to 3.08)	0.05 (−0.22 to 0.33)	.71
Fine motor	40.22 ± 15.89	39.18 ± 15.84	1.44 (−2.18 to 5.06)	0.11 (−0.16 to 0.38)	.43
Problem solving	44.17 ± 12.00	45.35 ± 12.38	−1.19 (−4.35 to 1.97)	−0.11 (−0.39 to 0.18)	.46
Personal-social	50.41 ± 8.90	49.19 ± 9.38	1.23 (−1.32 to 3.77)	0.14 (−0.15 to 0.44)	.34
Total score	224.71 ± 43.84	223.19 ± 43.90	1.52 (−9.02 to 12.06)	0.04 (−0.24 to 0.32)	.78

TABLE 3 ASQ Scores for the Exposed and Nonexposed Groups: Nonmatched Analysis

	Exposed Group, n =162	Nonexposed Group, n = 146	Difference		
	Raw Score, Mean ± SD	Raw Score, Mean ± SD	Raw Score, Mean (95% CI)[a]	Effect Size, Mean (95% CI)[a]	P
Communication	43.15 ± 14.19	41.75 ± 15.59	0.89 (−1.92 to 3.70)	0.07 (−0.15 to 0.30)	.53
Gross motor	46.50 ± 12.24	48.07 ± 10.96	−1.70 (−4.13 to 0.73)	−0.16 (−0.39 to 0.07)	.17
Fine motor	39.70 ± 16.16	38.53 ± 15.73	1.13 (−1.88 to 4.14)	0.08 (−0.14 to 0.31)	.46
Problem solving	43.42 ± 12.94	45.18 ± 12.58	−1.65 (−4.43 to 1.13)	−0.14 (−0.36 to 0.09)	.24
Personal-social	50.04 ± 9.63	49.36 ± 9.82	0.68 (−1.36 to 2.73)	0.07 (−0.15 to 0.29)	.51
Total score	221.36 ± 47.09	223.02 ± 45.24	−1.60 (−10.95 to 7.75)	−0.04 (−0.26 to 0.19)	.74

[a] Adjusted for number of questionnaire, gestational age, gender, adjusted age, ethnicity, and parental educational level.

and neurologic status in children fulfilling the same criteria as in the current study.[3,4,9–18] The children's age at follow-up varied from 3 months[17] to 18 years.[10,16] Most authors found normal development and IQ,[4,9,10,12,14,15,18] although Seidman et al[16] observed an increased risk of IQ <85 among 17-year-old male draftees with a neonatal TSB level >20 mg/dL (340 μmol/L). The results regarding minor neurologic dysfunction are more varied: some show an effect;[9,11,17] others do not.[3,4,12,14,15,18] These different findings may be related to the study design.

With the exception of the study by Newman et al,[3,4] only a small number of children had a TSB level >25 mg/dL in the previously mentioned studies. In their controlled study of 140 5-year-old children with a neonatal TSB level >25 mg/dL, Newman et al[3,4] found no associations between bilirubin exposure and neurologic abnormalities, IQ, behavioral problems, and frequencies of parental concern. Our data support the results of this powerful study.

Previous studies were based on clinical examinations or registry data.[3,4,9–18] Our study used questionnaires, because we expected this method would be adequate for evaluating a national cohort of children spread over a large geographical area. Moreover, parental involvement in the assessment of children's development is important because they have a profound knowledge of the child, and their concerns are useful indicators of the children's developmental status.[22,23] Parental questionnaires have been shown to give developmental assessments similar to formal tests.[19,20]

We consider it a strength that our study was population based and had a fairly high response rate. The exposed group was well described. The cohort was population based, and there were no differences between participants and nonparticipants, which supports the generalizability of the results. It is also relevant that the ASQ is a way to evaluate the general development of children, and it encompasses an evaluation of motor development. It is especially important in this study, because the major symptom of chronic bilirubin encephalopathy is impaired motor function. We are not able to draw conclusions about more specific developmental problems such as attention-deficit/hyperactivity disorder and autism, however; these conditions have been suggested to be associated with neonatal hyperbilirubinemia in other studies.[13,24] We are not able to draw any conclusions concerning minor hearing loss, which is known to be linked to chronic bilirubin encephalopathy.[25]

A limitation of the study might be that the parents of children in the exposed group were anxious that their child might experience sequelae owing to the severe neonatal hyperbilirubinemia and therefore overestimated the child's abilities. We do not consider this option likely, however, because it is generally accepted that severe hyperbilirubinemia is reversible if the infant has no neurologic symptoms or very few neurologic symptoms in the neonatal period. Moreover, there is distance from the experience of the neonatal period for the parents because the hyperbilirubinemia episodes occurred 1 to 5 years ago. Chronic bilirubin encephalopathy is

TABLE 4 Effect Estimates of Potential Confounders of the ASQ Total Score

	Raw Score	Effect Size	P
	Mean (95% CI)	Mean (95% CI)	
Group			
Exposed	−1.60 (−10.95 to 7.75)	−0.04 (−0.26 to 0.19)	.74
Nonexposed	Reference	Reference	
Gestational age			
35–37 wk	6.99 (−3.45 to 17.43)	0.17 (−0.08 to 0.42)	.19
38–42 wk	Reference	Reference	
Gender			
Male	−21.09 (−30.57 to −11.61)	−0.50 (−0.73 to −0.28)	<.001
Female	Reference	Reference	
Parental education group			
Primary school	Reference	Reference	
High school/college	2.12 (−9.19 to 13.43)	0.05 (−0.22 to 0.32)	.71
University education	11.76 (0.29 to 23.23)	0.28 (0.01 to 0.55)	.04
Ethnicity			
Non-Caucasian	−6.27 (−22.73 to 10.19)	−0.15 (−0.54 to 0.24)	.45
Caucasian	Reference	Reference	

The estimates also were corrected for number of questionnaire and adjusted age.

related more closely to the serum concentration of reserve albumin for binding of bilirubin[26]; however, measurement of this concentration is still experimental, and TSB level is the parameter used in clinical practice.

Recent data from Denmark reveal that the incidence of extreme neonatal hyperbilirubinemia has increased during the past 10 years.[27] Because this condition still carries a large risk of long-term neurologic sequelae, infants with intermediate or advanced acute bilirubin encephalopathy[28] should be monitored closely.

CONCLUSIONS

Using the parent-completed ASQ, we observed no association between bilirubin exposure and the overall development in children between 1 and 5 years of age with a neonatal TSB level ≥25 mg/dL and no symptoms or only minor symptoms of acute bilirubin encephalopathy.

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