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Neonatal Hyperbilirubinemia and Risk of Autism Spectrum Disorders

Lisa A. Croen, PhD*; Cathleen K. Yoshida, MS*; Roxana Odouli, MSPH*; and Thomas B. Newman, MD, MPH†

ABSTRACT. *Objective.* To investigate the association between neonatal hyperbilirubinemia and autism spectrum disorders (ASD).

Methods. We conducted a large case-control study nested within the cohort of singleton term infants born between 1995 and 1998 at a northern California Kaiser Permanente hospital. Case subjects ($n = 338$) were children with an ASD diagnosis recorded in Kaiser Permanente outpatient databases; control subjects ($n = 1817$) were children without an ASD diagnosis, who were randomly sampled and frequency-matched to case subjects according to gender, birth year, and birth hospital.

Results. Approximately 28% of case and control subjects received ≥ 1 bilirubin test in the first 30 days of life. No case-control differences were observed for maximal bilirubin levels of ≥ 15 mg/dL (10.1% vs 12.1%), ≥ 20 mg/dL (2.1% vs 2.5%), or ≥ 25 mg/dL (0.3% vs 0.2%). Compared with children whose maximal neonatal bilirubin levels were < 15 mg/dL or not measured, children with any degree of bilirubin level elevation were not at increased risk of ASD, after adjustment for gender, birth facility, maternal age, maternal race/ethnicity, maternal education, and gestational age (for bilirubin levels of 15-19.9 mg/dL: odds ratio: 0.7; 95% confidence interval: 0.5-1.2; for bilirubin levels of 20-24.9 mg/dL: odds ratio: 0.7; 95% confidence interval: 0.3-1.6; for bilirubin levels of ≥ 25 mg/dL: odds ratio: 1.1; 95% confidence interval: 0.1-11.2).

Conclusion. These data suggest that neonatal hyperbilirubinemia is not a risk factor for ASD. *Pediatrics* 2005;115:e135-e138. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1870; *autism spectrum disorders, hyperbilirubinemia, jaundice, pervasive developmental disorder, neonatal risk.*

ABBREVIATIONS. PDD-NOS, pervasive developmental disorder not otherwise specified; ASD, autism spectrum disorders; KP, Kaiser Permanente; ICD-9-CM, *International Classification of Diseases, 9th Revision, Clinical Modification.*

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Autism is a behaviorally defined, neurodevelopmental disorder characterized by impairments in social interaction, abnormalities in verbal and nonverbal communication, and restricted stereotyped interests and behaviors.¹ Although the causes of autism are not well understood, both genetic and nongenetic factors are thought to play roles.^{2,3} Evidence from neuroimaging, neuropathologic, and epidemiologic studies provides support for the concept that aberrant brain development in the prenatal and early postnatal periods underlies the pathogenesis of autism. The most consistently reported neuropathologic findings include decreased numbers of Purkinje cells in the cerebellum, increased cell packing density and smaller neuronal size in the limbic system, and features of cortical dysgenesis or migration disturbances.⁴

Although neonatal jaundice is generally benign, very high neonatal bilirubin levels can cause kernicterus and somewhat lower levels were associated with more subtle sequelae in some studies.⁵⁻¹¹ The most well-established toxic effects of bilirubin on the central nervous system involve the basal ganglia and auditory nuclei. Cognitive function is generally relatively spared, even among children with kernicterus. To our knowledge, deficits in social interaction among children with kernicterus, beyond those attributable to their motor and auditory disabilities, have not been reported.

There has been concern that shorter postpartum stays and less aggressive jaundice treatment in the past several years might have resulted in increased incidences of extreme hyperbilirubinemia and its sequelae.^{12,13} During the same period, the reported prevalence of autism spectrum disorders (ASD) has increased dramatically,¹⁴ although it is not clear how much of this increase represents a true change in the occurrence of the disorders.

Several studies examined the relationship between autism and various obstetric and neonatal complications previously associated with fetal neurologic impairment, including neonatal jaundice,¹⁵⁻²² and a few reported positive associations.^{15,21} The results of those studies have been difficult to interpret, however, because of limitations in study design, including non-population-based study samples, small sample sizes, inadequate comparison groups, reliance on parental reports of jaundice rather than documentation in medical records, and lack of control for potential confounding factors in statistical analyses.

This study was undertaken to address the limita-

tions of previous studies in assessing the potential role of neonatal jaundice as a risk factor for autism. An association between neonatal hyperbilirubinemia and ASD could have important implications for prevention, because hyperbilirubinemia is a common, potentially modifiable, risk factor. In addition, the absence of an association would be important to document, because neonatal hyperbilirubinemia and its treatment may produce anxiety among parents, especially if the possibility of brain damage attributable to high bilirubin levels is mentioned. By chance alone, ASD sometimes occur among children known to have experienced significant neonatal hyperbilirubinemia, and parents and clinicians caring for such children might wonder whether there is an association between the 2 conditions.

METHODS

We conducted a large, population-based, case-control study within an integrated health plan with extensive computerized data resources involving prospectively collected laboratory results and diagnoses. Case and control subjects were identified from the cohort of infants who were born at a northern California Kaiser Permanente (KP) facility between January 1995 and December 1998 and remained KP members for ≥ 2 years after birth ($n = 73\,291$). The KP medical care program is a large managed-care organization that provides care for >3.2 million residents of northern California, representing $\sim 30\%$ of the insured population in the region.

Case subjects ($n = 393$) were defined as children for whom an ASD diagnosis, ie, autism (*International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM]²³ code 299.0), Asperger's syndrome (ICD-9-CM code 299.8), or pervasive developmental disorder not otherwise specified (PDD-NOS) (ICD-9-CM code 299.8), was recorded in the KP outpatient clinical databases at any time between January 1995 and December 2002. All children were between 4 and 7 years of age at the time the databases were scanned. We randomly selected 5 control subjects per case subject, from the cohort of children who did not have a diagnosis of ASD recorded in the outpatient clinical databases ($n = 1965$). Control subjects were frequency-matched with case subjects according to gender, birth year, and hospital of birth. The final study sample was restricted to singleton infants born at gestational ages of >35 weeks for whom information on neonatal bilirubin levels was available.

Information on neonatal hyperbilirubinemia was derived from serum bilirubin test results recorded in the KP Regionwide Integrated Laboratory Information System, which contains the date, time, and results of all laboratory tests performed for KP patients.²⁴ The maximal bilirubin level (in milligrams per deciliter)

was defined as the highest recorded bilirubin level in the first 30 days of life. Data on phototherapy were derived from the computerized inpatient databases, which contain detailed information on diagnoses and procedures, as well as dates and locations of patient visits. Compared with chart review, we found this data source to be 94% sensitive and 100% specific.²⁵

Maternal age at delivery and child gender, gestational age, and birth weight were determined from information recorded in KP inpatient databases. Data on maternal race/ethnicity (white non-Hispanic, white Hispanic, black, Asian, or other) and maternal educational attainment at delivery (less than high school, high school graduate, college, postgraduate, or unknown) were obtained from the State of California birth certificate databases.

Differences in categorical variables between case subjects and control subjects were compared with χ^2 statistics. Differences in continuous variables were assessed with t tests. The risks of autism associated with maximal bilirubin levels above various cutoff points were estimated as odds ratios and 95% confidence intervals with multivariate logistic regression analyses. Infants for whom no bilirubin measurements were made were assumed to have levels below the cutoff points. Maternal and infant characteristics associated with maximal bilirubin levels and infant case status were included as covariates in multivariate analyses. All study procedures were approved by the KP Northern California Institutional Review Board and the California State Committee for the Protection of Human Subjects.

RESULTS

Characteristics of the 338 case subjects and 1817 control subjects in the final study population are shown in Table 1. The gestational age and birth weight distributions were similar for the case and control subjects. Male subjects outnumbered female subjects by 4 to 1 among case subjects, with a similar distribution among control subjects because of matching. The mean age at delivery was greater for case mothers, compared with control mothers ($P = .0001$), and case mothers averaged more years of education ($P = .0001$, rank-sum test).

Similar proportions of case (27.8%) and control (27.5%) infants underwent ≥ 1 bilirubin measurement in the first 30 days after birth ($P = .9$). Among those tested, there was no difference in the mean number of total serum bilirubin tests per infant, the maximal bilirubin level measured, or the proportion of infants who received phototherapy (Table 2).

Crude and adjusted odds ratios associated with maximal bilirubin levels of ≥ 15 mg/dL, ≥ 20 mg/dL, and ≥ 25 mg/dL are presented in Table 3. Regardless

TABLE 1. Description of Study Population, KP Singleton Term Births Occurring in 1995–1998

	Autism Case Subjects ($n = 338$)	Control Subjects ($n = 1817$)	P
Male, %	84	82	.47
Gestational age, wk, mean \pm SD	39.3 \pm 1.3	39.4 \pm 1.3	.17
Birth weight, g, mean \pm SD	3550 \pm 537	3542 \pm 505	.77
Maternal age, y, mean \pm SD	31.0 \pm 5.5	29.7 \pm 5.7	.0001
Maternal education, no. (%)			.0001*
Less than high school	20 (5.9)	171 (9.4)	
High school	70 (20.8)	524 (28.9)	
College	181 (53.7)	864 (47.7)	
Postgraduate	64 (19.0)	231 (12.8)	
Unknown	2 (0.6)	21 (1.2)	
Maternal race/ethnicity, no. (%)			.19
White non-Hispanic	172 (50.9)	821 (45.2)	
White Hispanic	57 (16.9)	407 (22.4)	
Black	30 (8.9)	158 (8.7)	
Asian	36 (10.7)	194 (10.7)	
Other	43 (12.7)	237 (13.0)	

* Derived with Wilcoxon rank-sum test.

TABLE 2. Frequency of Bilirubin Testing, Bilirubin Levels, and Phototherapy

	No. (%)		P
	Autism Case Subjects	Control Subjects	
≥1 bilirubin test	94 (27.8)	499 (27.5)	.90
No. of bilirubin tests per baby tested, mean ± SD	2.5 ± 2.0	2.7 ± 2.0	.62
Maximal reported bilirubin level of			
≥10 mg/dL	68 (20.1)	387 (21.3)	.63
≥15 mg/dL	34 (10.1)	220 (12.1)	.28
≥20 mg/dL	7 (2.1)	46 (2.5)	.62
≥25 mg/dL	1 (0.3)	3 (0.2)	.61
Baby received phototherapy	13 (3.8)	61 (3.4)	.65
Maximal bilirubin level of ≥20 mg/dL and baby received phototherapy	3 (0.9)	26 (1.4)	.43

TABLE 3. Unadjusted and Adjusted Odds Ratios for ASDs Associated With Various Maximal Neonatal Bilirubin Levels

Maximal Bilirubin Level*	No.		OR _c (95% CI)	OR _a (95% CI)
	Autism Case Subjects (N = 338)	Control Subjects (N = 1817)		
≥15 mg/dL vs <15 mg/dL	34	220	0.81 (0.55–1.19)	0.67 (0.43–1.05)
≥20 mg/dL vs <20 mg/dL	7	46	0.81 (0.36–1.82)	0.69 (0.28–1.69)
≥25 mg/dL vs <25 mg/dL	1	3	1.80 (0.19–17.33)	1.22 (0.12–12.68)

OR_c indicates crude odds ratio; CI, confidence interval; OR_a, adjusted odd ratio, adjusted for gender, birth facility, maternal age, maternal race/ethnicity, maternal education, and gestational age.

* No bilirubin testing was performed for 244 case subjects and 1318 control subjects; levels were assumed to be <15 mg/dL.

of the cutoff point used, elevated bilirubin levels in the first 30 days of life were not associated with a risk of autism. Similarly, compared with infants with maximal bilirubin levels of <15 mg/dL or not measured, infants with maximal bilirubin levels of 15 to 19.9 mg/dL, 20.0 to 24.9 mg/dL, or ≥25 mg/dL were not at increased risk for autism (Table 4).

DISCUSSION

Our findings of no association between neonatal bilirubin levels and ASD are strengthened by our large, population-based, study sample, the use of prospectively collected laboratory measurements of total serum bilirubin levels, physician-documented diagnoses of ASD, the use of an appropriately matched internal comparison group, and the use of multivariate analytic techniques to adjust for several important covariates. One important limitation of this study is the lack of validation of the ASD diagnoses with standardized clinical assessments. For a sample of 35 children with ASD diagnoses recorded in the KP outpatient databases, we conducted a review of all pediatric and mental health records with a protocol closely adapted from the Metropolitan Atlanta Developmental Disabilities Surveillance

Program.²⁶ We abstracted detailed information on diagnoses, school services, verbatim descriptions of behaviors associated with autism, developmental histories, and psychometric assessment results. All 35 children were determined to have an ASD, 19 (54%) according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria and 46% according to the clinical determination of a developmental pediatrician specializing in ASD, who performed an expert review of all abstracted data. Because diagnostic information contained in the outpatient databases often is not specific regarding the ASD subtype, we were not able to examine associations separately for autistic disorder, Asperger's syndrome, and PDD-NOS.

Most previous studies of the association between hyperbilirubinemia and autism included hyperbilirubinemia only as part of an obstetric suboptimality score, did not adequately define cutoff values for hyperbilirubinemia, or relied on parental reports of jaundice. Although several studies reported no association,^{16–18,20,22} a few suggested that hyperbilirubinemia occurred more frequently than expected among children later diagnosed with autism. Juul-Dam et al¹⁵ reported significant associations of PDD-

TABLE 4. Unadjusted and Adjusted Odds Ratios for ASDs Associated With Maximal Neonatal Bilirubin Levels of >15 mg/dL

Maximal Bilirubin Level*	No.		OR _c (95% CI)	OR _a (95% CI)
	Autism Case Subjects (N = 338)	Control Subjects (N = 1817)		
<15 mg/dL	304	1597	Ref	Ref
15–19.9 mg/dL	27	174	0.82 (0.53–1.25)	0.74 (0.48–1.15)
20–24.9 mg/dL	6	43	0.73 (0.31–1.74)	0.66 (0.27–1.59)
≥25 mg/dL	1	3	1.76 (0.18–16.91)	1.12 (0.11–11.15)

OR_c indicates crude odds ratio; CI, confidence interval; OR_a, adjusted odd ratio, adjusted for gender, birth facility, maternal age, maternal race/ethnicity, maternal education, and gestational age.

* No bilirubin testing was performed for 244 case subjects and 1318 control subjects; levels were assumed to be <15 mg/dL.

NOS ($n = 13$) and autism ($n = 51$) with hyperbilirubinemia. After adjustment for multiple comparisons, only PDD-NOS remained significantly associated. The prevalence of hyperbilirubinemia, defined as bilirubin levels of >10 mg/dL, was 54% among children with PDD-NOS and 22% among children with autism, compared with 12% reported for the Collaborative Perinatal Project 30 years earlier.⁵ In a different study of 23 children diagnosed with infantile autism,²¹ the frequency of serum bilirubin levels of >16 mg/dL (13.0%) was significantly greater than the expected rate of occurrence (3%) reported in a 1975 textbook. In our study population, 21% of control subjects had documented total serum bilirubin levels of ≥ 10 mg/dL and 10% had levels of ≥ 16 mg/dL. These differences in the reported prevalence of hyperbilirubinemia in different populations underscore the need for internal comparison groups in etiologic studies.

Screening for neonatal hyperbilirubinemia is not routine; rather, it is performed at the discretion of clinicians. It is possible that maximal bilirubin levels were underestimated for some of the untested infants in our study, resulting in nondifferential misclassification and possibly biasing results toward the null hypothesis. It is very unlikely that many infants with bilirubin levels of >20 mg/dL would not have been tested, however, and the effect of misclassification would thus only mask a real association at low maximal bilirubin levels (<20 mg/dL). We were unable to examine the risk associated with the length of hyperbilirubinemia.

CONCLUSION

These results suggest that neonatal hyperbilirubinemia is not a risk factor for ASD.

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