Risk of Autism Associated With Hyperbilirubinemia and Phototherapy

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abstract

OBJECTIVE: Whether neonatal hyperbilirubinemia and/or phototherapy increase the risk of autism spectrum disorder (ASD) is unclear. We sought to quantify the risk of ASD associated with elevated total serum bilirubin (TSB) levels and with phototherapy.

METHODS: In a retrospective cohort study of 525 409 infants born at ≥35 weeks' gestation in 15 Kaiser Permanente Northern California (KPNC) hospitals, 1995–2011, we obtained all TSB levels and determined which infants received phototherapy. From the KPNC Autism Registry, we identified patients with ASD diagnosed at a KPNC Autism Center, by a clinical specialist, or by a pediatrician. We calculated Cox proportional hazard ratios (HRs) for time to diagnosis of ASD, adjusting for confounding factors.

RESULTS: Among infants in the birth cohort, 2% had at least 1 TSB level ≥20 mg/dL, and 8% received phototherapy. The rate of ASD was 13 per 1000 births. Crude analyses revealed an association between TSB ≥20 and ASD (relative risk: 1.4; 95% confidence interval [CI]: 1.1–1.6), and between phototherapy and ASD (relative risk: 1.7; 95% CI: 1.5–1.8). After adjusting for confounders, TSB ≥20 (HR: 1.09; 95% CI: 0.89–1.35) and phototherapy (HR: 1.10; 95% CI: 0.98–1.24) were no longer significantly associated with ASD. Independent risk factors for ASD included maternal and paternal age; maternal and paternal higher education; male sex; birth weight <2500 g or ≥4200 g; and later year of birth.

CONCLUSIONS: After adjustment for the effects of sociodemographic factors and birth weight, neither hyperbilirubinemia nor phototherapy was an independent risk factor for ASD.

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Dr Wu performed data analysis and interpretation of data, and drafted the initial manuscript; Dr Kuzniewicz assisted with obtaining funding, supervised data management and creation of Kaiser Permanente Northern California (KPNC) data sets, and reviewed and revised the manuscript; Dr Croen supervised data management and creation of KPNC autism data sets and reviewed and revised the manuscript; Ms Walsh coordinated the study and reviewed the manuscript; Dr McCulloch provided statistical and design consultation, assisted with obtaining funding, and reviewed and revised the manuscript; Dr Newman conceptualized, designed, and led efforts to obtain funding for the study, analyzed data, and reviewed and critically revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: The etiology of autism spectrum disorder (ASD) is poorly understood. Neonatal jaundice has been associated with ASD in some previous studies. Whether this association is causal, and whether phototherapy modifies the risk of ASD, is unknown.

WHAT THIS STUDY ADDS: Hyperbilirubinemia and phototherapy were both associated with increased risk of ASD on bivariate analysis. However, after adjustment for the confounding effects of sociodemographic factors, neither hyperbilirubinemia nor phototherapy was a significant independent risk factor for ASD.

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interaction, deficits in verbal and nonverbal communication, and restricted and stereotyped interests and behaviors. The etiology of ASD is complex, involving both genetic and environmental risk factors. It is hypothesized that environmental insults occurring during early brain development can lead to ASD among infants who are genetically vulnerable.[1–4]

Neonatal hyperbilirubinemia, or jaundice, has been implicated as a potential environmental risk factor for ASD.[5,6] Hyperbilirubinemia is associated with a 43% increased risk of ASD, based on a meta-analysis of 13 studies (odds ratio: 1.43; 95% confidence interval [CI]: 1.22–1.67).[5] Yet previous studies of hyperbilirubinemia and ASD have important limitations. Past studies relied on administrative diagnoses or parental report of jaundice instead of analyzing total serum bilirubin (TSB) levels[7–11]; evaluated a dichotomous hyperbilirubinemia variable based on traditional cutoffs or infant weight[12–15]; did not control for confounding[9,11,16,17]; were not population-based[9,16,17]; or included a relatively small sample ($N < 120$) of children with ASD.[10,16,17] Thus, the heterogeneity ($P = .002$)[5] and limitations of previous studies limit the conclusions that can be drawn.

Phototherapy is the standard treatment of neonatal hyperbilirubinemia. Yet in vivo and in vitro studies suggest that phototherapy can lead to DNA damage, altered cytokine levels, and increased oxidative stress,[18–20] mechanisms suggested in the pathophysiology for ASD. Whether phototherapy impacts the risk of ASD has not been studied. It is important to determine whether this common treatment reduces the risk of ASD, or may in fact contribute to an increased ASD risk. In a large population of term and near-term infants, we set out to quantify the excess risk of ASD in newborns exposed to hyperbilirubinemia, and to determine whether phototherapy is independently associated with ASD.

METHODS

We performed a retrospective cohort study as part of the Late Impact of Getting Hyperbilirubinemia or Phototherapy study.[21,22] The Late Impact of Getting Hyperbilirubinemia or Phototherapy study includes 525 409 infants born at ≥35 weeks' gestation at 15 Kaiser Permanente Northern California (KPNC) hospitals between January 1, 1995, and December 31, 2011. KPNC is an integrated community medical care delivery system that serves 3.9 million members, constituting ~40% of the insured population of Northern California. The study was approved by the California Committee for Human Subjects (for birth certificate data), and by the institutional review boards at KPNC and University of California, San Francisco.

We excluded infants who died during the birth hospitalization ($N = 344$, 0.07%), whose birth hospitalization ended with a transfer out of the KPNC system ($N = 891$, 0.17%), or who were followed <60 days ($N = 24\,532$, 4.7%). We further excluded infants with at least 2 inpatient or outpatient physician diagnoses of the following *International Classification of Diseases, Ninth Revision* (ICD-9) conditions: Down syndrome (758.0, $N = 531$), other chromosomal abnormalities (758.1–758.9, $N = 680$), or congenital anomalies diagnosed at <15 days (740–759.9 except 743.65 [nasolacrimal passage anomaly], $N = 41\,388$). After these exclusions, the final study cohort consisted of 457 855 infants.

Predictors

We obtained all TSB levels from electronic medical records up to age 30 days. We assumed that the 49% of infants who did not receive any TSB measurements did not have significant jaundice, and grouped them with those with TSB <10 mg/dL. We classified the highest single TSB value for each infant into the following categories: TSB <10 mg/dL or not measured; 10 to 14.9 mg/dL; 15 to 19.9 mg/dL; or ≥20 mg/dL. We excluded TSB levels in which the direct or conjugated bilirubin measurement constituted over 50% of the total, because such levels suggest liver disease and because the conjugated bilirubin would not be expected to cross the blood brain barrier.

We determined which infants received in-hospital or home phototherapy. For the 80% of children born before implementation of the Epic (Verona, WI) electronic medical record, we identified those who received inpatient phototherapy from procedure codes (99.82 and 99.83) for admissions before age 30 days. For children born after implementation of EPIC, we classified infants as having received inpatient phototherapy if they had either a phototherapy nursing flow sheet or both a procedure code and an order for phototherapy. Use of home phototherapy was determined from the KPNC durable medical equipment database.

From KPNC electronic data sources, we abstracted covariates including maternal age, maternal race/ethnicity, infant sex, gestational age, birth weight, 5-minute Apgar score, year, and hospital of birth. From linked birth certificate data, we collected information regarding paternal age, and maternal and paternal education.

Outcome

We used the KPNC Autism Registry[12,23–25] to identify subjects who had been diagnosed with ASD either by an ASD evaluation center, by a clinical ASD specialist outside

TABLE 1 Sociodemographic Factors Associated With Hyperbilirubinemia

	Maximum TSB Level, %		
	≥20 mg/dL, *N* = 8677	<20 mg/dL, *N* = 449 178[a]	*P*
Race/ethnicity			
White	34	42	<.0005
Asian	34	18	<.0005
African American	4	8	<.0005
Hispanic	22	24	<.0005
Other or missing	6	7	.03
Maternal age ≥30 y	54	50	<.0005
Maternal college education[b]	70	65	<.0005
Male sex	60	50	<.0005
Gestational age <38 wk	26	11	<.0005

[a] TSB <20 mg/dL or not measured.

[b] Includes some college or more.

the ASD center (ie, psychiatrist, psychologist, or developmental pediatrician), or by a general pediatrician. ASD was defined as a diagnosis of autism (ICD-9 299.0), Asperger syndrome (ICD-9 299.8), or pervasive developmental disorder not otherwise specified (ICD-9 299.9). The ASD centers provide evaluation, diagnosis, and treatment planning for KP children and adolescents. Children suspected of having an ASD are generally referred by their pediatrician to an ASD center, where they are evaluated by using a standardized protocol, including the Autism Diagnostic Observation Schedule,[26] by a multidisciplinary clinical team including child and adolescent psychiatrists and psychologists, general and developmental pediatricians, and speech and occupational therapists. We retrieved all ASD diagnoses made during the years January 1, 1995–June 30, 2015. Thus all children in the birth cohort were at least 3.5 years of age at the time that we abstracted data from the Autism Registry.

Statistical Analysis

We calculated crude incidence rates by dividing ASD cases by person-years of follow-up, and CIs for comparing incidence rate ratios by using exact binomial calculations. Follow-up for each study subject began at birth and ended at the date of first diagnosis of ASD, death, or last date of membership within the health plan through June 30, 2015, whichever came first.

We used a Cox proportional hazards model to evaluate the independent associations between hyperbilirubinemia and ASD, and phototherapy and ASD. We calculated hazard ratios (HRs) and exact 95% CIs for categories of TSB and for phototherapy, adjusting for potential confounders. In sensitivity analyses, we ran separate models in which hyperbilirubinemia was defined as follows: TSB >25, and TSB > American Academy of Pediatrics 2004 phototherapy treatment threshold for age and risk group, based on gestational age and direct antiglobulin test results, as previously described.[27] In addition, we examined the effect of phototherapy by using a phototherapy propensity score among only infants who had a TSB level within 3 mg/dL of the American Academy of Pediatrics phototherapy threshold, as previously described.[28] This allowed us to adjust for TSB levels before but not after phototherapy, thus allowing us to investigate whether phototherapy might reduce the risk of autism by preventing hyperbilirubinemia. We performed all analyses by using Stata version 12 (Stata Corp, College Station, TX).

RESULTS

Among 457 855 infants in the birth cohort, 2% had a maximum TSB level ≥20 mg/dL. The remaining infants had a maximum TSB level <10 mg/dL or not measured (70%), 10 to 14.9 mg/dL (16%), or 15 to 19.9 mg/dL (12%). Infants with a TSB ≥20 mg/dL were more likely to be male, Asian, <38 weeks' gestational age, and to be born to a mother who was over 30 years old and who had at least some college education (Table 1).

Hyperbilirubinemia decreased in frequency in the later years of the study; that is, a TSB level ≥20 mg/dL was present in 2.1% of infants born in 1995–2000, 2.0% in 2001–2006, and 1.5% in 2007–2011. This was expected because of the adoption of universal bilirubin screening within KPNC between 2004 and 2007, which led to increased recognition and treatment of elevated bilirubin levels, resulting in a lower rate of significant hyperbilirubinemia during the later years of the study.[29]

Phototherapy was used to treat 8% of all patients in the birth cohort. The rate of phototherapy varied by maximum TSB level as follows: TSB <10 mg/dL or not measured: 0.4%; TSB 10 to 14.9 mg/dL: 14%; TSB 15 to 19.9 mg/dL: 31%; TSB ≥20 mg/dL: 69%. Use of phototherapy increased during the study years as follows: 3% in 1995–2000; 7% in 2001–2006; and 13% in 2007–2011.

Overall incidence of ASD in the birth cohort was 13 per 1000 births. Increasing TSB levels and phototherapy were both significantly associated with risk of ASD in bivariate analyses (Table 2).

After adjusting for potential confounders, TSB ≥20 (HR: 1.09; 95% CI: 0.89–1.35) and phototherapy (HR: 1.10; 95% CI: 0.98–1.24) were no longer significantly associated with ASD (Table 3). Independent risk factors for ASD included increasing maternal and paternal age; higher degrees of maternal and paternal

TABLE 2 Crude Incidence Rate Ratios for Autism Based on Maximum TSB Levels, Phototherapy, and Sociodemographic Characteristics, in a 1995–2011 California Birth Cohort

	N at Risk	*N* With Autism	Incidence per 1000	Incidence per 1000 Person-Years	Crude Incidence Rate Ratio	95% CI Lower	95% CI Upper	*P*
Total population	457 855	5979	13	1.63	—	—	—	—
Highest TSB, mg/dL[a]								
Not done or <10	322 246	3952	12	1.29	Ref	—	—	—
10–14.9	71 593	1033	14	1.82	1.41	1.31	1.51	<.0005
15–19.9	55 339	848	15	1.89	1.47	1.36	1.58	<.0005
≥20	8677	146	17	1.74	1.35	1.14	1.59	.001
Phototherapy								
No	423 403	5399	13	1.38	Ref	—	—	—
Yes	34 452	580	17	2.32	1.7	1.54	1.834	<.0005
Maternal age, y								
<30	230 858	2448	11	1.16	Ref	—	—	—
≥30	226 997	3531	16	1.72	1.48	1.40	1.55	<.0005
Paternal age, y								
<40	379 677	4641	12	1.34	Ref	—	—	—
≥40	58 196	1097	19	2.08	1.55	1.45	1.66	<.0005
Maternal education								
High school or less	154 449	1508	10	1.14	Ref	—	—	—
College or more	281 620	4255	15	1.85	1.63	1.54	1.72	<.0005
Paternal education								
High school or less	175 611	1830	10	1.20	Ref	—	—	—
College or more	255 982	3867	15	1.85	1.54	1.46	1.62	<.0005
Race/ethnicity								
White	192 954	2678	14	1.51	Ref	—	—	—
Asian	85 713	1262	15	1.64	1.09	1.02	1.16	.02
African American	36 037	414	11	1.16	0.78	0.70	0.86	<.0005
Hispanic	110 933	1202	11	1.20	0.80	0.75	0.86	<.0005
Other or missing	32 218	423	13	1.61	1.07	0.96	1.19	.20
Infant sex								
Female	226 885	1112	5	0.54	Ref	—	—	—
Male	230 970	4867	21	2.33	4.35	4.08	4.65	<.0005
Gestational age, wk								
<38	53 158	799	15	1.40	1.2	1.13	1.31	<.0005
≥38	404 697	5180	13	1.71	Ref	—	—	—
Birth weight, g								
<2500	14 577	222	15	1.71	1.22	1.06	1.40	.005
2500–4199	413 143	5239	13	1.40	Ref	—	—	—
≥4200	30 135	518	17	1.83	1.31	1.19	1.43	<.0005
Apgar at 5 min								
<7	3660	63	17	1.95	1.36	1.05	1.75	.02
7–10	454 195	5916	13	1.43	Ref	—	—	—
Year of birth								
1995–2000	155 088	1806	12	0.91	Ref	—	—	
2001–2006	164 410	2329	14	1.59	1.8	1.65	1.87	<.0005
2007–2011	138 357	1844	13	2.60	2.86	2.68	3.06	<.0005

[a] To convert to μmol/L, multiply by 17.1.

education (ie, some college or more); male infant; abnormally low and high birth weight; and later year of birth. In contrast, infants born to mothers of African American, Hispanic, and Asian race/ethnicity had a reduced risk of ASD after adjusting for confounders (Table 3).

Separate multivariate models performed as part of sensitivity analyses confirmed that alternative definitions of hyperbilirubinemia (ie, TSB >25 mg/dL and TSB above the American Academy of Pediatrics phototherapy threshold) were also not independent risk factors for ASD after adjusting for confounders. Propensity-adjusted models revealed neither benefit nor harm from phototherapy (HR: 1.09; 95% CI: 0.95–1.24). Entering maternal and paternal education in 4 categories (ie, eighth grade or less, some high school, some college, postgraduate) did not change the results appreciably.

DISCUSSION

In this large retrospective cohort study, elevated TSB levels and phototherapy were both associated

TABLE 3 Multivariate HRs for Autism in a 1995–2011 Birth Cohort

Variable[a]	HR	Lower	Upper	*P*
Highest TSB, mg/dL[b]				
Not done or <10	Ref	—	—	—
10–14.9	1.06	0.98	1.14	.14
15–19.9	1.07	0.98	1.17	.14
≥20	1.09	0.89	1.35	.41
Phototherapy	1.10	0.98	1.24	.12
Maternal age, y	1.02	1.01	1.02	<.0005
Paternal age, y	1.02	1.01	1.02	<.0005
Maternal college education[c]	1.22	1.13	1.31	<.0005
Paternal college education[c]	1.13	1.05	1.21	.001
Race/ethnicity, maternal				
White	Ref	—	—	
Asian	0.86	0.80	0.93	<.0005
African American	0.89	0.79	1.00	.048
Hispanic	0.82	0.76	0.89	<.0005
Other	0.86	0.77	0.96	.01
Male sex	4.29	4.01	4.59	<.0005
Gestational age <38 wk	1.07	0.98	1.17	.13
Birth weight, g				
<2500	1.22	1.05	1.42	.01
2500–<4200	Ref	—	—	—
≥4200	1.16	1.05	1.27	.003
Apgar <7 at 5 min	1.18	0.90	1.54	.22
Year of birth				
1995	Ref	—	—	—
1996	1.03	0.86	1.22	.78
1997	1.10	0.93	1.31	.27
1998	1.33	1.12	1.57	.001
1999	1.41	1.12	1.67	<.0005
2000	1.50	1.27	1.78	<.0005
2001	1.60	1.36	1.90	<.0005
2002	1.81	1.54	2.14	<.0005
2003	2.16	1.84	2.54	<.0005
2004	1.83	1.55	2.17	<.0005
2005	2.13	1.81	2.51	<.0005
2006	2.15	1.82	2.53	<.0005
2007	2.00	1.69	2.38	<.0005
2008	2.79	2.36	3.29	<.0005
2009	2.82	2.38	3.34	<.0005
2010	3.54	2.99	4.20	<.0005
2011	3.85	3.22	4.60	<.0005

[a] Cox model includes all variables in the table, as well as hospital of birth.
[b] To convert to μmol/L, multiply by 17.1.
[c] Includes some college or more.

with ASD in bivariate analyses. However, after adjustment for the confounding effects of sociodemographic factors, neither hyperbilirubinemia nor phototherapy remained a significant independent risk factor for ASD.

ASD is a growing public health concern whose underlying pathogenesis is poorly understood. The lifetime cost to support an individual with ASD in the United States is $1.4 to $2.4 million, amounting to a total societal cost of $61 billion per year.[30] Although genetic factors play an important role, a recent study suggests that environmental factors explain over half of the liability for ASD.[31] Potential epigenetic changes[2–4] induced by environmental in utero stressors such as exposure to medications,[32,33] hazardous air pollutants,[34,35] and excessive smoking in early pregnancy[36] constitute an active area of ASD etiologic research.

Neonatal hyperbilirubinemia is a potentially modifiable factor. Concerns have been raised that elevated bilirubin may increase the risk of a child developing the social and communication deficits that characterize autism.[5,37–39] A recent review of 18 relevant clinical studies identified 7 publications that revealed a significant association between hyperbilirubinemia and ASD on bivariate analysis.[37] Our findings suggest that these previously reported associations may not represent a true causal relationship.[40] That is, factors that increase the risk of both hyperbilirubinemia and ASD, such as male sex and lower gestational age, are likely responsible for the previously described link between hyperbilirubinemia and ASD. Among 13 studies that were combined in a meta-analysis that suggested a link between jaundice and ASD, only 6 studies controlled for potential confounders, and 5 of these 6 studies were limited by either no TSB values available, jaundice definitions based on birth weight, or recall bias due to the use of parental questionnaires to determine the presence of jaundice.[5]

Our findings corroborate several known sociodemographic risk factors for ASD, including advanced parental age and education, male sex, lower gestational age, and low birth weight.[41–44] After adjusting for confounders such as maternal age and education, the rate of ASD was lower in Asians, African Americans, and Hispanics than in whites. Others have also reported a lower rate of ASD in African Americans and Hispanics.[16,41,42,45] It remains unclear whether this reflects a true disparity in the occurrence of ASD, or whether there are differences in diagnostic practices and access to services leading to decreased and delayed recognition of ASD in some racial/ethnic groups,[46] thus providing an underestimate of ASD in certain groups.

The rate of ASD increased almost fourfold between 1995 and 2011.

This trend is consistent with other reports. Prevalence estimates of ASD have grown exponentially from ≤0.5 per 1000 in the 1970s and 1980s, to 1 to 2 per 1000 in the 1990s,[47] to 14.7 per 1000 based on the latest US active surveillance data from 2010.[41] Some studies suggest that changes in the definition of ASD, an increased public awareness of this condition, and increased availability of specialized services for ASD leading to a preferential diagnosis of ASD over other diagnoses such as mental retardation (ie, intellectual disability) and learning disabilities, together account for much of this dramatic rise in ASD over the past 2 decades.[48–50] In addition, KPNC established 3 regional ASD evaluation centers in 2004–2008, and an early developmental screening program initiated in selected facilities in 2009 became fully implemented by 2012. These 2 programs resulted in more children being diagnosed with ASD at earlier ages.

Although neonatal hyperbilirubinemia is almost always benign, extremely high bilirubin levels can cause cerebral palsy and sensorineural hearing loss.[51–53] The lack of evidence in our study that hyperbilirubinemia causes ASD is an important finding because neonatal jaundice is a common occurrence that may produce anxiety among parents and clinicians, especially when caring for an infant who already carries an increased genetic risk of ASD (eg, having a sibling with ASD[54]). It is similarly reassuring that phototherapy does not appear to be associated with an increased risk of ASD, based on our data.

Strengths of our study include the large study population; the availability of comprehensive measurements of TSB and lack of recall bias; the ability to adjust for multiple sociodemographic confounders; the evaluation of hyperbilirubinemia using different cutoffs and definitions; and the ability to separate the effects of hyperbilirubinemia from phototherapy, which is possible because of variability in the treatment of hyperbilirubinemia within KPNC.

A limitation of our study was the reliance on physician diagnoses of ASD, as opposed to using a systematic and standardized diagnostic assessment across the entire population. However, 62% of children with ASD were diagnosed at a KPNC ASD center, and among those who were diagnosed outside of an ASD center, ASD was documented in their KPNC medical record on 2 or more occasions in 60%. Based on a large study of 1272 KP members <18 years of age, 2 or more ASD diagnoses recorded in the medical record was a strong predictor of a valid ASD diagnosis, with a positive predictive value of 87%.[55]

We lacked data regarding dose of phototherapy, and the measured maximum TSB levels are only estimates of the true peak exposure levels. Our study is also subject to residual confounding by factors such as breastfeeding. Although breastfeeding is a known risk factor for hyperbilirubinemia, definitive evidence is lacking for an association between breastfeeding and ASD.[56] However, if breastfeeding were protective of ASD, then not including it in the multivariable analysis would lead to an underestimate of the effect of hyperbilirubinemia on ASD.

CONCLUSIONS

Within a large US birth population, we found no evidence that hyperbilirubinemia or phototherapy play a role in the pathogenesis of ASD.

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ABBREVIATIONS

ASD: autism spectrum disorder
CI: confidence interval
HR: hazard ratio
ICD-9: *International Classification of Diseases, Ninth Revision*
KPNC: Kaiser Permanente Northern California
TSB: total serum bilirubin

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