Childhood Seizures After Phototherapy

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abstract

BACKGROUND AND OBJECTIVES: In a recent Danish study, researchers found an increased risk of childhood epilepsy after phototherapy but only in boys. We investigated this association in a Kaiser Permanente Northern California cohort.

METHODS: From 499 642 infants born at ≥35 weeks' gestation in 1995–2011 followed for ≥60 days, we excluded 1773 that exceeded exchange transfusion thresholds and 1237 with seizure diagnoses at <60 days. We ascertained phototherapy, covariates, and outcomes from electronic records and existing databases. Our primary outcome was ≥1 encounter with a seizure diagnosis plus ≥1 prescription for an antiepileptic drug. We used Cox and Poisson models to adjust for bilirubin levels and other confounding variables.

RESULTS: A total of 37 683 (7.6%) infants received any phototherapy. The mean (SD) follow-up time was 8.1 (5.2) years. The crude incidence rate per 1000 person-years of the primary outcome was 1.24 among phototherapy-exposed children and 0.76 among those unexposed (rate ratio: 1.63; 95% confidence interval [CI]: 1.44 to 1.85). The adjusted hazard ratio (aHR) was 1.22 (95% CI: 1.05 to 1.42; $P = .009$). Boys were at higher risk of seizures overall (aHR = 1.18; 95% CI: 1.10 to 1.27) and had a higher aHR for phototherapy (1.33; 95% CI: 1.10 to 1.61) than girls (1.07; 95% CI: 0.84 to 1.37), although effect modification by sex was not statistically significant ($P = .17$). The adjusted 10-year excess risks per 1000 were 2.4 (95% CI: 0.6 to 4.1) overall, 3.7 (95% CI: 1.2 to 6.1) in boys, and 0.8 (95% CI: −1.7 to 3.2) in girls.

CONCLUSIONS: Phototherapy in newborns is associated with a small increased risk of childhood seizures, even after adjusting for bilirubin values, and the risk is more significant in boys.

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WHAT'S KNOWN ON THIS SUBJECT: In a recent Danish cohort study, researchers found that boys (but not girls) who had received phototherapy for neonatal jaundice had approximately double the risk of subsequent epilepsy, approximately an 8 per 1000 excess risk over 10 years.

WHAT THIS STUDY ADDS: In this large cohort, with better ability to adjust for confounding variables, we confirmed this association, but it was weaker: a 30% to 40% adjusted increase in risk in boys, approximately a 4 per 1000 excess risk over 10 years.

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Phototherapy is commonly used to treat jaundice in newborns. Although the most important goal of phototherapy is to prevent a high total serum bilirubin (TSB) level from reaching a level that might be neurotoxic or require exchange transfusion,[1] phototherapy is also used at lower TSB levels, with a goal of preventing readmissions for phototherapy.[2] In some studies, authors have also linked more modest TSB elevations to subtle neurodevelopmental problems.[3–6] Phototherapy might also be used with a goal of preventing these problems.

Whether phototherapy is a reasonable treatment to prevent bilirubin toxicity depends on the safety profile and potential toxicity of phototherapy itself. In previous studies, researchers have linked phototherapy to future risk of diabetes,[7] autism,[8] and cancer,[9,10] but researchers in these studies have not controlled for neonatal bilirubin levels. As part of the Late Impact of Getting Hyperbilirubinemia or photoTherapy (LIGHT) study,[11] we have examined associations between phototherapy and these previously reported adverse outcomes and have not found any statistically significant associations after adjustment for bilirubin levels and other confounding factors.[12–14]

In a recent study from Denmark,[15] authors reported a significant increased risk of epilepsy after phototherapy (adjusted hazard ratio [aHR]: 1.66; 95% confidence interval [CI]: 1.23 to 2.24), which appeared to be confined to boys (aHR: 1.98; 95% CI: 1.40 to 2.78). However, in that study, researchers were unable to control for possible confounding by bilirubin levels. We sought to investigate the association between phototherapy and the development of seizures and epilepsy in the LIGHT study, controlling for bilirubin levels and other potential confounders.

METHODS

Design, Subjects, and Human Subjects Approval

The study was performed by using data from Kaiser Permanente Northern California (KPNC), an integrated health care system providing health care to ∼4.1 million members in Northern California. The LIGHT cohort included 499 642 children born at ≥35 weeks' gestation from January 1, 1995, through December 31, 2011, at 1 of 15 KPNC hospitals who were discharged alive from their birth hospital and followed >60 days after birth.[12] We excluded 1773 infants whose TSB level ever exceeded the American Academy of Pediatrics (AAP) exchange transfusion threshold[1] using Direct Antiglobulin Test (DAT) results and gestational age to determine the neurotoxicity risk group, as previously described.[16] To reduce the possibility of including subjects with seizures caused by perinatal events that might also lead to phototherapy, we also excluded 1237 subjects with any encounter before 60 days that included a diagnosis of epilepsy or convulsions (*International Classification of Diseases, Ninth Revision* [ICD-9] codes 345–345.9, 779.0, and 780.3–780.39), leaving a cohort of 496 632 infants.

The institutional review boards for the protection of human subjects at the University of California, San Francisco (10-04918) and KPNC (CN-10MKuzn-03-H) approved the study.

Predictor Variables

For children born before the implementation of KPNC's electronic medical record system (80% of subjects), we ascertained inpatient phototherapy using hospital discharge procedure codes (99.82 and 99.83) for hospitalizations that began <30 days after birth. For children born after the transition to electronic records, we used physician orders and nursing phototherapy flow sheets. We ascertained home phototherapy on the basis of an order for a home phototherapy device. Because we did not have reliable data on the duration or intensity of phototherapy, the primary predictor variable for all analyses was a dichotomous variable for any phototherapy, whether delivered in the hospital, at home, or both.

We obtained covariates from electronic records, including sex, parent-reported infant race and/or ethnicity, birth weight, gestational age, and TSB levels. We defined small for gestational age (SGA) as a birth weight below the 10th percentile for gestational age in this cohort. To optimize control for confounding by indication, we assessed each TSB level in relation to the 2004 AAP phototherapy guidelines,[1] determining the neurotoxicity risk group as described above.

We created indicator variables for Down syndrome, other chromosomal abnormalities, and congenital anomalies using ICD-9 codes as described in an earlier study.[14] We also created indicator variables for encounters with any of the following diagnoses at <60 days: birth asphyxia or hypoxic ischemic encephalopathy (ICD-9 codes 768.5–768.9), intracranial hemorrhage (772.1–772.2), or meningitis (ICD-9 codes listed in Supplemental Table 5).

We used quantile regression to create a variable indicating whether the newborn's birth hospitalization length of stay was >90th percentile expected for gestational age, birth weight, delivery mode, and phototherapy exposure.

Outcome Variables

We used the KPNC virtual data warehouse[17] to identify subjects with encounters, generating an ICD-9 code for any seizure (345 to 345.91 and 780.3 to 780.39). We grouped

these as follows: febrile seizures (780.31, 780.32), seizures or epilepsy not coded as febrile (345–345.91, 780.3, 780.39; hereafter referred to as "seizures"), and epilepsy (345–345.91). We further subdivided the epilepsy diagnoses into generalized (345.00–345.3, 345.60), partial (345.4–345.51), and unspecified (345.80–345.91) epilepsy; the same child may have had encounters with more than 1 of these groups of epilepsy diagnoses.

We obtained dates of prescriptions for antiepileptic drugs (AEDs) from the KPNC Pharmacy Information System. The AEDs first prescribed and their frequencies are included in Supplemental Table 6.

For each subject, we defined distinct encounters as occurring on different days or on the same day if they were of different encounter types (ambulatory visits, emergency department visits, admissions, or deaths) or in different departments (eg, pediatrics or neurology). Our primary outcome variable was having at least 1 encounter with a seizure diagnosis plus at least 1 prescription for an AED. Secondary outcomes were other combinations of ≥1 or ≥2 encounters with seizure or epilepsy diagnoses and ≥1 prescriptions for AEDs. For outcomes that required 2 encounters or 1 encounter plus a prescription for an AED, the outcome date was the date of the second required event.

Follow-up Time

Length of follow-up varied in this study, both because some subjects left the KPNC health care system and because follow-up began at birth (1995–2011) but ended in 2014 for all subjects. For purposes of quantifying incidence rates and using proportional hazards models, follow-up for each member of the cohort began at age 60 days and ended at death, the date they qualified as having the outcome of interest, or the last follow-up date, defined as the last day of the last calendar month of coverage by the KPNC health plan or the last encounter date through March 11, 2014.

Statistical Analysis

We calculated crude incidence rates and incidence rate ratios (IRRs) by dividing cases with the outcome by person-years of follow-up, comparing incidence rates using 2-tailed exact significance tests. We used multivariable Cox proportional hazards models to obtain HRs for phototherapy and covariates. We included covariates on the basis of electronic availability and biological plausibility or statistical significance. All multivariable analyses included indicator variables for hospital of birth.

In addition, we performed 2 sets of propensity-adjusted analyses, as previously described in detail.[14] Restricted propensity analyses included only those (N = 97 336) with at least 1 TSB level between −3 and +4.9 mg/dL from the appropriate AAP phototherapy threshold. In these analyses we controlled for the first such level in 1-mg/dL categories. For inclusive propensity analyses we included all subjects and controlled for bilirubin levels using only a dichotomous variable indicating whether any TSB level had exceeded the AAP phototherapy threshold, coded 0 if no TSB was measured. We controlled for propensity scores in deciles.

We used Poisson models to estimate the 10-year marginal excess risks and 95% CIs of those treated with phototherapy, as previously described.[12,14] We used Stata 14.2 (StataCorp, College Station, TX) for all analyses.

RESULTS

Cohort Description and Crude Incidence and Hazard Rates

Of the 496 632 children in the cohort, 37 683 (7.6%) ever received phototherapy. The majority received only hospital phototherapy (6.1%), 1.0% received only home phototherapy, and 0.5% received both. As previously described,[14] use of phototherapy increased during the study period in this cohort, from 2.4% in 1995 to 15.9% in 2011, leading to shorter mean (SD) follow-up time of 6.1 (4.2) years among those who received phototherapy compared with 8.3 (5.2) years among those who did not. The demographic and clinical characteristics of the cohort are as previously described, except that the exclusion of 1773 subjects with TSB levels exceeding exchange levels led to slightly smaller proportions of subjects with hyperbilirubinemia risk factors and exposure to phototherapy than in previous reports (Table 1).

The primary outcome of ≥1 seizure diagnosis and ≥1 AED prescription occurred in 3153 (0.63%) subjects. The crude incidence rates per 1000 person-years were 1.24 among those exposed to phototherapy and 0.76 among those unexposed (crude IRR: 1.63; 95% CI: 1.44 to 1.85; P < .0001). The mean (SD) age at the time of primary outcome ascertainment was 5.0 (4.4) years. The excess risk associated with phototherapy increased over time (Fig 1). Other relatively prevalent predictors of future seizures in unadjusted analyses included male sex, African American race, lower gestational age, low birth weight, and being SGA (Table 1).

Unadjusted HRs were, in most cases, similar to crude IRRs (Tables 1 and 2, first 3 columns). Maximum bilirubin levels of 20 to 24.9 mg/dL (but not lower levels) were associated with seizures in unadjusted analyses but less strongly so than phototherapy.

Multivariable Analyses

In a Cox model with adjustment for the variables in Table 2, the

TABLE 1 Description of the Cohort and Crude Incidence and Crude IRRs for the Outcome of at Least 1 Seizure Diagnosis Plus at Least 1 AED Prescription by Demographic and Clinical Characteristics

	N at Risk	*N* With Outcome	Incidence per 1000 Person-y	Crude IRR (95% CI)	*P*
Total population	496 632	3153	0.79		
1995–2000	164 623	1455	0.74	Reference	—
2001–2006	177 167	1114	0.79	1.07 (0.99 to 1.16)	.076
2007–2011	154 842	584	0.94	1.27 (1.16 to 1.41)	<.0001
Maternal age, y					
<25	107 671	733	0.82	Reference	—
≥25	388 961	2420	0.78	0.95 (0.87 to 1.03)	.2143
Sex					
Female	242 879	1403	0.72	Reference	—
Male	253 753	1750	0.86	1.2 (1.12 to 1.29)	<.0001
Race and/or ethnicity					
White	210 280	1401	0.81	Reference	—
Asian American	92 997	500	0.68	0.84 (0.76 to 0.93)	.0009
African American	38 797	371	1.10	1.36 (1.21 to 1.52)	<.0001
Hispanic	119 766	733	0.77	0.95 (0.87 to 1.04)	.27
Other	34 792	148	0.60	0.74 (0.62 to 0.88)	.0003
Down syndrome	511	15	3.77	4.8 (2.68 to 7.93)	<.0001
Chromosomal anomaly other than trisomy 21	647	98	18.9	24.67 (19.96 to 30.17)	<.0001
Congenital anomaly	9814	160	2.47	3.25 (2.76 to 3.82)	<.0001
Gestational age, wk					
<38	58 556	472	1.05	1.38 (1.25 to 1.52)	<.0001
≥38	438 076	2681	0.76	Reference	—
Birth wt, g					
<2500	16 650	200	1.53	2.01 (1.73 to 2.32)	<.0001
≥2500	479 982	2953	0.76	Reference	—
Size for gestational age					
Small (<10th percentile)	49 122	397	1.00	1.31 (1.17 to 1.45)	<.0001
Appropriate or large	447 510	2756	0.76	Reference	—
Cesarean delivery					
No	385 895	2384	0.75	Reference	—
Yes	110 737	769	0.93	1.23 (1.13 to 1.34)	<.0001
5-min Apgar <7					
No	492 635	3109	0.78	Reference	—
Yes	3997	44	1.42	1.81 (1.31 to 2.44)	.0003
DAT result					
Not done	310 504	2007	0.74	0.83 (0.77 to 0.89)	<.0001
Negative	175 628	1078	0.89	Reference	—
Positive	10 500	68	0.89	0.99 (0.77 to 1.27)	.98
Conjugated bilirubin ≥1.0 mg/dL	2116	33	2.07	2.64 (1.82 to 3.72)	<.0001
Maximum TSB, mg/dL					
<10	102 485	500	0.85	Reference	—
10–14.9	79 533	496	0.91	1.07 (0.94 to 1.21)	.28
15–19.9	61 472	401	0.93	1.1 (0.96 to 1.26)	.16
20–24.9	8022	78	1.15	1.35 (1.05 to 1.72)	.016
Not done	245 120	1678	0.71	0.84 (0.76 to 0.93)	.0008
Any phototherapy					
No	458 949	2870	0.76	Reference	—
Yes	37 683	283	1.24	1.63 (1.44 to 1.85)	<.0001
Phototherapy dose					
None	459 949	2870	0.76	Reference	—
Home only	5027	15	0.59	0.77 (0.43 to 1.27)	.32
1 admission	31 893	263	1.33	1.74 (1.53 to 1.98)	<.0001
≥2 admissions	763	5	1.30	1.71 (0.55 to 4)	.25

HR for phototherapy was reduced to 1.22 (95% CI: 1.05 to 1.42) but remained statistically significant ($P = .009$).

We did several analyses to address the possibility of confounding by indication due to either TSB levels or to other variables associated with newborn illness as reflected in longer length of stay. The crude HR of 1.45 (95% CI: 1.14 to 1.84; $P = .001$) for a maximum TSB level of 20 to 24.9 mg/dL declined and was no longer statistically significant (HR: 1.29, 95% CI: 0.99 to 1.69; $P = .06$) in the multivariate model that included phototherapy (Table 2). This was entirely due to inclusion of phototherapy; omitting only phototherapy from the model increased the HR for a TSB level of 20 to 24.9 mg/dL back to 1.46 (95% CI: 1.13 to 1.87; $P = .003$).

Similarly, when we substituted a dichotomous variable indicating whether the infant ever had a TSB level exceeding the AAP phototherapy threshold for the 5-category maximum TSB level, the HR for having a TSB level exceeding the AAP phototherapy threshold was only 1.05 (95% CI: 0.89 to 1.25). That HR increased to 1.20 (95% CI: 1.04 to 1.39) when phototherapy was omitted from the model. Finally, omitting infants whose birth hospitalization length of stay was >90th percentile did not diminish the aHR for phototherapy (HR: 1.25; 95% CI: 1.06 to 1.48), again suggesting it is the phototherapy itself rather than its indication that increases the risk of seizures.

The effects of phototherapy in both the restricted propensity model (HR 1.22; 95% CI: 1.01 to 1.48) and the inclusive propensity model (HR 1.23; 95% CI: 1.05 to 1.45) were similar to those of the Cox model shown in Table 2.

TABLE 1 Continued

	N at Risk	*N* With Outcome	Incidence per 1000 Person-y	Crude IRR (95% CI)	*P*
Diagnoses made at <60 d					
Meningitis	367	4	1.25	1.59 (0.43 to 4.08)	.36
Birth asphyxia/ hypoxic ischemic encephalopathy	1182	13	1.22	1.55 (0.83 to 2.66)	.13
Intracranial hemorrhage	173	7	5.28	6.71 (2.69 to 13.84)	.0001

IRR, incidence rate ratio; —, not applicable.

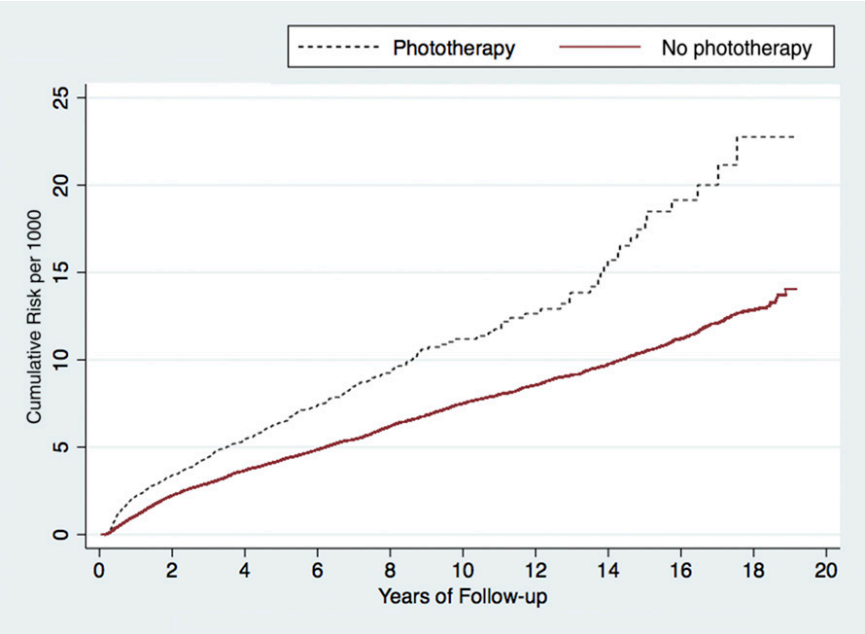

FIGURE 1
Kaplan-Meier (unadjusted) cumulative incidence curves for the outcome of ≥1 encounter with a seizure diagnosis plus ≥1 AED prescription.

For our primary outcome, the association was statistically significant in boys (HR: 1.33; 95% CI: 1.10 to 1.61, $P < .004$) but not in girls (HR 1.07; 95% CI: 0.84 to 1.37, $P = .59$). We examined several secondary outcomes, both in the entire cohort and separately in boys and girls (Table 3). Febrile seizures were not significantly associated with phototherapy. For the outcomes requiring only ≥1 seizure encounter not coded as febrile, *P* values for phototherapy in fully adjusted models were <.0001. We did not find any type of epilepsy that was more strongly associated with phototherapy exposure, although sample sizes for different epilepsy subgroups were smaller, so CIs were wider.

HRs of phototherapy for all types of seizures were higher for boys, and no seizure outcome was statistically significantly associated with phototherapy in girls (Table 3). Formal tests for effect modification by sex were not statistically significant; the lowest *P* values were .09 for at least 2 seizure encounters and .07 for at least 1 encounter with a generalized seizure epilepsy diagnosis (Table 3). There was no evidence of effect modification by race or gestational age.

Results were not sensitive to choice of multivariable model. A logistic model with indicator variables for year of birth (to address unequal follow-up time) and the other variables in Table 2 yielded an adjusted odds ratio for phototherapy of 1.20 (95% CI: 1.03 to 1.40; $P = .02$). A Poisson model with the variables in Table 2 yielded an adjusted IRR of 1.23 (95% CI: 1.06 to 1.43; $P = .007$).

The marginal adjusted 10-year excess risks from the Poisson model decreased with decreasing frequency of the outcome, from ~7 per 1000 for ≥1 seizure encounter to ~2 per 1000 for ≥1 epilepsy diagnosis plus ≥1 AED prescription (Table 4). Estimated adjusted 10-year excess risks in boys were higher than in girls by 1.9 to 6.6 per 1000, due to both the higher HRs for phototherapy in boys and boys' higher baseline risk of seizures.

DISCUSSION

In this large Northern California retrospective cohort study, we found a crude association (IRR: ~1.6; 95% CI: 1.44 to 1.85) between neonatal exposure to phototherapy and childhood seizures. This rate ratio was lower than the crude risk ratio for epilepsy of 2.18 (95% CI: 1.71 to 2.78) reported from Denmark[15] but similar in magnitude to the multivariate HR of 1.66 (95% CI: 1.23 to 2.24) from that study. With adjustment for bilirubin levels and other covariates, the HR declined to 1.22 (95% CI: 1.05 to 1.42) but remained statistically significant. The finding of a weak but statistically significant multivariate association between phototherapy and childhood seizures was robust to changes in how the seizure outcome was defined and to the method of statistical

TABLE 2 Crude and Multivariate aHRs for Phototherapy and Covariates for at Least 1 Seizure Diagnosis Plus at Least 1 AED Prescription

Variable	Crude HR	*P*	aHR (95% CI)	*P*
Any phototherapy	1.55	<.001	1.22 (1.05 to 1.42)	.009
Year of birth				
1995–2000	Reference	—	1	—
2001–2006	1.03	.57	1.01 (0.93 to 1.1)	.82
2007–2011	1.05	.44	0.98 (0.87 to 1.1)	.72
Maternal age in y, ≥25	0.94	.059	0.94 (0.86 to 1.02)	.16
Male sex	1.20	<.001	1.18 (1.1 to 1.27)	<.001
Race and/or ethnicity				
White	Reference	—	1	—
Asian American	0.84	.001	0.8 (0.72 to 0.9)	<.001
African American	1.37	<.001	1.3 (1.15 to 1.47)	<.001
Hispanic	0.95	.25	0.94 (0.86 to 1.03)	.19
Other	0.72	<.001	0.71 (0.6 to 0.84)	<.001
Down syndrome	4.77	<.001	1.38 (0.82 to 2.33)	.23
Chromosomal anomaly other than trisomy 21	24.7	<.001	16.42 (13.2 to 20.43)	<.001
Congenital anomaly	3.15	<.001	2.1 (1.77 to 2.49)	<.001
Gestational age, wk				
35	1.96	<.001	1.33 (1.05 to 1.69)	.02
36	1.63	<.001	1.29 (1.07 to 1.55)	.008
37	1.20	.001	1.06 (0.92 to 1.24)	.42
38	1.15	.021	1.08 (0.97 to 1.21)	.16
39	1.09	.098	1.06 (0.97 to 1.17)	.19
40	Reference	—	1	—
41	0.96	.53	0.92 (0.82 to 1.04)	.20
≥42	0.82	.15	0.76 (0.55 to 1.05)	.098
Birth wt <2500 g	2.00	<.001	1.28 (1.06 to 1.54)	.01
SGA	1.31	<.001	1.14 (1.01 to 1.29)	.028
Delivery mode				
Spontaneous vaginal	Reference	—	1	—
Assisted vaginal	1.09	.197	1.06 (0.93 to 1.2)	.41
Cesarean	1.23	<.001	1.13 (1.04 to 1.23)	.005
Unspecified	1.58	<.001	1.47 (0.95 to 2.29)	.086
5-min Apgar score <7	1.80	.009	1.4 (1.03 to 1.89)	.03
DAT result				
Not done	0.86	<.001	0.95 (0.88 to 1.04)	.26
Negative	Reference	—	1	—
Positive	1.00	.97	0.98 (0.76 to 1.25)	.84
Maximum conjugated bilirubin ≥1 mg/dL	2.62	<.001	1.43 (1 to 2.05)	.05
Maximum TSB, mg/dL				
<10	Reference	—	1	—
10–14.9	1.11	.14	1.03 (0.9 to 1.17)	.68
15–19.9	1.14	.21	1.07 (0.92 to 1.23)	.38
20–24.9	1.45	.001	1.29 (0.99 to 1.69)	.061
Not done	0.91	.16	0.98 (0.88 to 1.1)	.76
Meningitis	1.61	.26	1.41 (0.53 to 3.76)	.49
Birth asphyxia or hypoxic ischemic encephalopathy	1.59	.16	1.12 (0.64 to 1.94)	.69
Intracranial hemorrhage	6.69	<.001	2.39 (1.12 to 5.1)	.024

aHR, adjusted hazard ratio; —, not applicable.

adjustment. As was reported in the Danish study,[15] we found no association between phototherapy and febrile seizures.

The lower HRs for phototherapy in the current study compared with those previously reported from Denmark could be due to better control for confounding variables, including TSB levels. It is also possible that the dose of phototherapy was higher in Denmark, where only 4.5% of the infants were treated, compared with an average of 7.6% in the current study. Finally, on the basis of the overlapping CIs, some of the difference could be due to chance.

Although the effect modification by sex was not statistically significant for any outcome at $P < .05$, it is striking that the effect of phototherapy was seen only in boys, as was previously reported in Denmark. Male sex itself was associated with approximately a 20% increased risk of seizures, so even if the HR was the same in boys and girls, the excess risk and clinical importance would be greater in boys because of their higher baseline risk.

Strengths of this study include the large sample size, the ability to control for bilirubin levels and many other covariates, and objective measurements of outcome, including prescriptions for AEDs. Limitations include lack of information on the dose or type of phototherapy given and reliance on ICD-9 codes for some covariates and to classify seizure types. This study did not include data on breastfeeding, which has been reported to be associated with decreased risk of epilepsy.[18,19] However, we would expect effects of breastfeeding on phototherapy use to be primarily related to the higher TSB levels seen in breastfed newborns, and we controlled for TSB levels in multivariable analyses.

The low *P* values and the study design make chance and bias unlikely explanations for the association. This leaves the possibility of confounding; that is, the possibility that something that led to phototherapy exposure is the actual cause of the increased risk of childhood seizures. In 2 previous studies, researchers have linked neonatal jaundice, the main indication for phototherapy, to

TABLE 3 Overall and Sex-Specific aHRs for Phototherapy and Different Outcomes

Outcome	*N* With Outcome	aHR (95% CI), All	aHR (95% CI), Boys	aHR (95% CI), Girls	*P* for Sex and Phototherapy Effect Modification
Febrile seizures					
≥1 encounter	9916	1.07 (0.99 to 1.16)	1.09 (0.98 to 1.21)	1.06 (0.93 to 1.2)	.81
Seizures not coded as febrile					
≥1 encounter	9908	1.2 (1.09 to 1.31)	1.28 (1.14 to 1.43)	1.08 (0.94 to 1.25)	.16
≥2 encounters	5365	1.22 (1.08 to 1.37)	1.31 (1.13 to 1.53)	1.09 (0.89 to 1.32)	.09
≥1 encounter + AEDs[a]	3153	1.22 (1.05 to 1.42)	1.33 (1.1 to 1.61)	1.07 (0.84 to 1.37)	.17
Epilepsy, all					
≥1 encounter	3551	1.3 (1.13 to 1.5)	1.41 (1.18 to 1.69)	1.14 (0.91 to 1.44)	.08
≥1 encounter + AEDs	2475	1.24 (1.05 to 1.47)	1.33 (1.07 to 1.64)	1.12 (0.85 to 1.46)	.22
Epilepsy NOS					
≥1 encounter	1997	1.39 (1.16 to 1.67)	1.49 (1.18 to 1.88)	1.25 (0.93 to 1.68)	.44
≥1 encounter +AEDS	1494	1.3 (1.05 to 1.6)	1.39 (1.07 to 1.82)	1.16 (0.83 to 1.63)	.07
Partial seizures					
≥1 encounter	1687	1.2 (0.97 to 1.47)	1.37 (1.05 to 1.78)	0.97 (0.69 to 1.36)	.33
≥1 encounter +AEDS	1376	1.08 (0.85 to 1.38)	1.2 (0.87 to 1.65)	0.93 (0.63 to 1.37)	.55
Generalized seizures					
≥1 encounter	1571	1.2 (0.96 to 1.49)	1.34 (1.02 to 1.77)	1.02 (0.72 to 1.44)	.07
≥1 encounter + AEDs	1165	1.21 (0.96 to 1.52)	1.31 (0.97 to 1.76)	1.06 (0.73 to 1.55)	.35

aHR, adjusted hazard ratio; AEDs, at least 1 prescription for antiepileptic drugs; NOS, not otherwise specified.
[a] Primary outcome.

TABLE 4 Ten-Year Adjusted Marginal Excess Risk (95% CI) of Seizure Outcomes per 1000, Overall and in Boys and Girls Treated With Phototherapy

Outcome	Overall Excess Risk (95% CI)	Excess Risk in Boys (95% CI)	Excess Risk in Girls (95% CI)
Seizures not coded as febrile			
≥1 encounter	6.8 (3.7 to 9.8)	9.7 (5.4 to 13.9)	3.1 (−1.2 to 7.4)
≥2 encounters	4 (1.7 to 6.3)	5.9 (2.7 to 9.1)	1.6 (−1.5 to 4.8)
≥1 encounter + AEDs[a]	2.4 (0.6 to 4.1)	3.7 (1.2 to 6.1)	0.8 (−1.7 to 3.2)
Epilepsy, all			
≥1 encounter	3.6 (1.7 to 5.6)	5.2 (2.4 to 8)	1.6 (−1.1 to 4.3)
≥1 encounter + AEDs	2 (0.4 to 3.6)	2.9 (0.7 to 5.2)	0.9 (−1.3 to 3.1)

[a] Primary outcome. AEDs: at least 1 prescription for AEDs.

epilepsy risk,[20,21] and the authors of the Danish study stressed the need for future studies in which researchers would include TSB levels. We found that maximum TSB levels and having at least 1 TSB level over the AAP phototherapy threshold were associated with future epilepsy risk but that these associations were no longer statistically significant when we included phototherapy in the model. On the other hand, the associations with phototherapy remained significant in both traditional and propensity-adjusted models that included different ways for controlling for bilirubin levels. These results suggest that associations between hyperbilirubinemia and seizures are largely due to phototherapy, rather than vice versa.

Confounding by unmeasured variables must be considered, particularly because the association is relatively weak. However, we cannot propose a plausible confounding variable that could explain the results. Decisions to treat with phototherapy are largely made on the basis of variables we included in multivariable analyses, including TSB levels for age and gestational age. It is particularly hard to imagine a confounder in boys only, that is, a risk factor for future epilepsy that would increase use of phototherapy in boys but not in girls.

How phototherapy might increase the risk of future seizures is not clear. There has been increasing concern that "bilirubin is not the only molecule likely to be affected by the application of light."[22] Phototherapy damages DNA,[23–28] generates free radicals and oxidative stress,[29–32] and alters cytokine levels.[33–35] Some combination of these might lead to neuronal or glial cell injury that could predispose to future seizures. The apparent greater susceptibility of boys, either to these phototherapy-induced injuries or to developing epilepsy as a result of them, is consistent with sex differences in susceptibility to perinatal injury and to various types of experimentally induced epilepsy reported in laboratory animals.[36–39]

Our results have important clinical implications. Although the adjusted

excess risks of epilepsy were modest, in the range of 2 to 7 per 1000 over 10 years, they are likely significant compared with projected benefits, particularly in infants whose TSB levels are below current treatment thresholds. Many such infants are treated prophylactically, in hopes of preventing a readmission for phototherapy.[2] The benefits of such treatment are unlikely to exceed the potential harm. In fact, with our results, we suggest the need to consider raising phototherapy thresholds, as some groups have already done.[40] Finally, although some researchers have suggested the possibility of neurotoxicity due to moderate levels of hyperbilirubinemia,[4,6,41,42] the results of this study suggest that using phototherapy to treat TSB levels lower than those required to prevent exchange transfusions may actually increase the risk of neurotoxicity.

CONCLUSIONS

We have confirmed a small increased risk of childhood seizures among children (particularly boys) exposed to neonatal phototherapy. The association does not appear to be due to hyperbilirubinemia or other known confounding variables.

ABBREVIATIONS

AAP: American Academy of Pediatrics
AED: antiepileptic drug
aHR: adjusted hazard ratio
CI: confidence interval
DAT: Direct Antiglobulin Test
HR: hazard ratio
ICD-9: *International Classification of Diseases, Ninth Revision*
IRR: incidence rate ratio
KPNC: Kaiser Permanente Northern California
LIGHT: Late Impact of Getting Hyperbilirubinemia or photoTherapy
SGA: small for gestational age
TSB: total serum bilirubin

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