Research Article

Cancer Epidemiology, Biomarkers & Prevention

Mode of Delivery and Risk of Childhood Leukemia

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Abstract

Background: Childhood infection and immune response have long been suspected in the etiology of childhood leukemia, specifically acute lymphoblastic leukemia (ALL). Normal primary inoculation of the core human microbiome is circumvented by cesarean section (CS) delivery, which is a proposed modulator of both immune response and early-life infection.

Methods: In this study, we examined CS delivery and the risk of childhood leukemia using data from the California Childhood Leukemia Study (CCLS) case–control study and additive logistic regression models.

Results: We observed no association between CS and acute myelogenous leukemia [OR, 0.96; 95% confidence interval (CI), 0.52–1.55]. We observed a suggestive association for ALL and CS (OR, 1.22; 95% CI, 0.97–1.54). When examining common ALL (cALL), defined as ALL with expression of CD10 and CD19 surface antigens and diagnosis occurring between 2 and 5.9 years of age, we found a significant association with CS (OR, 1.44; 95% CI, 1.0–2.06). ALL subjects that are not cALL showed a similar risk as ALL overall (OR, 1.15; 95% CI, 0.91–1.44). Because of previous findings suggesting effect modification, we stratified cALL subjects by Hispanic status. Although we observed no relationship for CS in non-Hispanics (OR, 1.14; 95% CI, 0.72–1.79), we did observe a strong association between cALL and CS in Hispanics (OR, 2.34; 95% CI, 1.23–4.46).

Conclusion: Within the CCLS, CS delivery seems to be associated with cALL and Hispanic subjects may be driving the association.

Impact: Further research combined with investigations into response to early infection and the microbiome is warranted. *Cancer Epidemiol Biomarkers Prev; 23(5); 876–81. ©2014 AACR.*

Introduction

Despite decades of research, the causes of the most common childhood cancer, acute leukemia, remain uncertain. It is clear that for the most common subtype of childhood leukemia, acute lymphoblastic leukemia (ALL), the preleukemic state is initiated *in utero* (1), yet a low concordance rate between monozygotic twins suggests a secondary trigger (2). One such proposed trigger is infection. Two related hypotheses posit etiologic mechanisms (2, 3). The delayed infection hypothesis of Greaves suggests that early-life immunologic isolation leads to aberrantly strong reactions to infection later in childhood, contributing to leukemia risk (4), whereas the population-mixing hypothesis of Kinlen suggests that leukemia is a rare response to infections that are new to a community (5). Commonly studied variables that are related to the timing of infection and associated with leukemia risk include daycare attendance and birth order and suggest that frequency and variety of exposures of infections reduces risk of ALL (6–8). Studies have shown that children developing any medically diagnosed infection (i.e., an infection leading to clinically fulminant symptoms) within the first year of life have an increased odds of developing common ALL (cALL) defined as ALL with expression of CD10 and CD19 surface antigens (pre–B-cell ALL) and diagnosis occurring between 2 and 5.9 years of age (9; 10). Recent work from our group showed significant differences in neonatal cytokines measured in Guthrie cards at birth between children who later contract ALL and controls (11). These findings suggest developmental differences in immune function might also contribute to development of disease.

Mounting evidence suggests a key role of the microbiome in human health, specifically induction of immune tolerance and adaptive and innate immune function (12, 13). Colonization of the microbiome occurs during the first moments of life (14, 15). Because mode of delivery has a profound impact on the earliest microbiome type of childbirth itself provides a surrogate measure of microbiome colonization (16). Three previous studies

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of cesarean section (CS) and childhood leukemia without examining subtypes of ALL reported no association (17–19). We cannot preclude the possibility of additional null findings that were not reported. A single previous study suggested an increase in odds of ALL associated with CS delivery (OR, 1.42; $P = 0.06$; ref. 20). The objective of this study is to determine whether risk of childhood leukemia is influenced by mode of delivery within a California population-based case–control study population and how this risk differs by leukemia subtype and Hispanic status.

Materials and Methods

The University of California Institutional Review Board and all participating institutions approved the study. Informed consent was obtained from all participating subjects.

The California Childhood Leukemia Study (CCLS) is described in detail elsewhere (21) Briefly, the CCLS is an ongoing case–control study in California, which commenced in 1995. The study began in the 17 counties surrounding the San Francisco Bay Area, and now (up to 2008) encompasses most of California through collaboration with 35 pediatric oncology centers in the state, allowing for rapid case ascertainment, usually within 72 hours from diagnosis. One or two controls are recruited using birth certificate information from the California Department of Public Health Office of Vital Records. Controls are matched on age, sex, Hispanic ethnicity, and maternal race.

In this analysis, we examined mode of delivery as reported on California birth certificates, approximately 93% of cases are born in California. Additional covariate information (breastfeeding, gestational age, income, gender, maternal race, and maternal ethnicity) was recorded during the conduct of the routine CCLS questionnaire either in person or over the phone depending on the phase of the study. This analysis includes 732 cases and 1,070 controls. Subjects with missing data (57 cases, 154 controls) on mode of delivery, gestational age, breastfeeding, or matching variables were excluded from the analysis. Subjects with Down syndrome (165) were excluded from all analyses. Cases were stratified by major subtype of leukemia; acute myelogenous leukemia (AML; $n = 85$), ALL ($n = 647$), and cALL ($n = 242$). cALL is defined as ALL with expression of CD10 and CD19 surface antigens (pre–B-cell ALL) and diagnosis occurring between 2 and 5.9 years of age.

We used logistic regression models to examine the relationship between leukemia and CS. Matched pairs were separated to include all controls and increase sample size. Covariates assessed as plausible confounders were identified by obstetrical consultants. Additive regression models were determined *a priori* and not changed during analysis. Logistic regression models were adjusted for the influence of matching factors, household income, gestational age, and breastfeeding. A subanalysis included separation of subjects by Hispanic status and cALL because previous research has shown effect modification in these subgroups specifically in factors relating to immune exposure and response (1, 22).

Results

Demographic variables were similar for cases and controls with the exception of household income (Table 1). This difference has been noted in previous CCLS studies as an artifact of control participant ascertainment and participation. Cases and controls did not differ significantly with regard to breastfeeding or gestational age.

Regression analyses of the three major subtypes of leukemia yielded varying results (Table 2). Logistic regression models showed marginally significant increased odds of CS in ALL subjects (OR, 1.22; $P = 0.09$) and statistically significant odds for subjects with cALL (OR, 1.44; $P = 0.05$). There was no observed effect of CS on AML (OR $= 0.96$, $P = 0.9$). None of the models were significantly influenced by breastfeeding or gestational age. Interactions were tested between all covariates; the only significant interaction identified was between CS and Hispanic status.

Because previous studies within the CCLS have shown a difference in incidence and risk of childhood leukemia in children of Hispanic origin compared with non-Hispanic whites and because a statistical interaction was observed, we stratified cALL cases and controls by Hispanic status (Table 3). Logistic regression analysis showed an increase in the odds of CS by a factor of 2.3 in Hispanic cALL subjects (OR, 2.34; $P = 0.009$), whereas a nonsignificant OR was observed in non-Hispanics cALL cases (OR, 1.14; $P = 0.56$). Lymphoid leukemias that did not meet the cALL case definition showed no significant association with CS delivery overall or if stratified by Hispanic status.

Discussion

Our results and the previous study by Kaye and colleagues, examining ALL and CS (20) provide evidence that birth by CS delivery is associated with an increased risk of ALL. These findings are in contrast with three studies that found no statistically significant association between CS and ALL. The observed differences in risk in these studies may be due to variations in characteristics of the study populations of two of the studies. Our study is the only study that specifically examined cALL, and we do not observe statistical significance in ALL overall until we stratify by leukemia subtype, suggesting that the cALL subtype is driving the association. The observation of increased odds of CS in Hispanic children diagnosed with cALL is intriguing but tenuous due to the small sample available. Further studies with larger samples are needed. National and global data show that Hispanics are at the highest risk

Table 1. Distribution of subjects in the CCLS

	ALL					cALL					AML				
Characteristics	Cases ($n = 647$)	%	Controls ($n = 1,070$)	%	*P*	Cases ($n = 242$)	%	Controls ($n = 578$)	%	*P*	Cases ($n = 85$)	%	Controls ($n = 1,070$)	%	*P*
Mean age at Dx (SE±)	5.12 (0.120)		5.20 (0.11)		0.66	3.41 (0.05)		3.79 (0.05)		0.15	5.55 (0.48)		5.20 (0.11)		0.47
Sex															
Male	378	58.4	626	58.5	1.00	145	59.9	337	58.3	0.73	43	50.6	626	58.5	0.19
Female	269	41.6	444	41.5		97	40.1	241	41.7		42	49.4	444	41.5	
Ethnicity														0.0	
Hispanic	279	43.1	423	39.5	0.16	101	41.7	231	40.0	0.69	34	40.0	423	39.5	1.00
Non-Hispanic	368	56.9	647	60.5		141	58.3	347	60.0		51	60.0	647	60.5	
Maternal race															
White/Caucasian	336	51.9	591	55.2		126	52.1	315	54.5		53	62.4	591	55.2	
African American	18	2.8	27	2.5		3	1.2	13	2.2		3	3.5	27	2.5	
Native American	11	1.7	17	1.6		7	2.9	9	1.6		1	1.2	17	1.6	
Asian/Pacific Islander	72	11.1	107	10.0		31	12.8	65	11.2		4	4.7	107	10.0	
Mixed/other	210	32.5	328	30.7		75	31.0	176	30.4		24	28.2	328	30.7	
Household income					<0.001					<0.001					<0.001
<15,000	94	14.5	98	9.2		38	15.7	50	8.7		16	18.8	98	9.2	
15,000–29,999	120	18.5	136	12.7		40	16.5	66	11.4		16	18.8	136	12.7	
30,000–44,999	99	15.3	134	12.5		38	15.7	75	13.0		9	10.6	134	12.5	
45,000–59,999	96	14.8	141	13.2		35	14.5	80	13.8		9	10.6	141	13.2	
60,000–74,999	45	7.0	114	10.7		14	5.8	59	10.2		11	12.9	114	10.7	
≥75,000	193	29.8	447	41.8		77	31.8	248	42.9		24	28.2	447	41.8	
Mean gestational age	39.22 (0.08)		39.17 (0.07)		0.46	39.30 (0.14)		39.15 (0.09)		0.36	39.34 (0.26)		39.17 (0.07)		0.53
Breastfeeding															
Yes	549	84.9	939	87.8	0.1	213	88.0	513	88.8	0.86	70	82.4	939	87.8	0.2
No	98	15.1	131	12.2		29	12.0	65	11.2		15	17.6	131	12.2	

Table 2. Mode of delivery by leukemia subtype

Subtype	Variable	Controls (*n*)	Cases (*n*)	Crude OR	95% CI	*P*	Adjusted OR[a]	95% CI[a]	Adjusted *P* value[a]
ALL	Vaginal	836	489	referent	—	—	referent	—	—
	Cesarean section	234	158	1.15	0.92–1.45	0.24	1.22	0.97–1.54	0.09
	Income	—	—	—	—	—	0.83	0.78–0.86	<0.001
	Gestational age	—	—	—	—	—	1.01	0.96–1.05	0.73
	Breastfeeding	—	—	—	—	—	0.93	0.70–1.25	0.63
		—	—	—	—	—	—	—	—
cALL	Vaginal	455	179	referent	—	—	referent	—	—
	Cesarean section	123	63	1.3	0.92–1.85	0.14	1.44	1.0–2.06	0.05
	Income	—	—	—	—	–	0.8	0.73–0.88	<0.001
	Gestational age	—	—	—	—	—	1.04	0.97–1.12	0.26
	Breastfeeding	—	—	—	—	—	1.14	0.71–1.88	0.59
		—	—	—	—	—	—	—	—
AML	Vaginal	836	68	referent	—	—	referent	—	—
	Cesarean section	234	17	0.89	0.52–1.55	0.79	0.96	0.54–1.66	0.9
	Income	—	—	—	—	—	0.81	0.71–0.92	<0.001
	Gestational age	—	—	—	—	—	1.02	09.3–1.15	0.6
	Breastfeeding	—	—	—	—	—	0.83	0.46–1.58	0.54

[a]All models adjusted for matching factors: age, sex, maternal race, and income.

for ALL (7). Interestingly, different ethnic groups seem to harbor unique compositions of bacteria within the mid-vagina with Hispanics exhibiting highly diverse bacteria and the highest vaginal pH of any ethnic group (23). These observations taken together suggest a different endemic microbial population and possibly varying circulating microorganisms by the social/ethnic group.

Perinatal exposures to microbes, determined largely by mode of delivery, result in significant differences in composition of gut microflora for the first 6 to 12 months of life (24). This period is critical in adaptive immune development. Pioneering studies point to a role of differential microbiome colonization in autoimmune disorders (25) and other chronic diseases (26, 27), and a probable role of the microbiome in the susceptibility to infection with pathogenic organisms (28).

Mode of delivery, particularly delivery by CS, has been investigated as a risk factor in other disorders. A meta-analysis of 23 studies of childhood asthma showed

Table 3. Mode of delivery in cALL subjects by Hispanic status

Hispanic status	Variable	Controls (*n*)	Cases (*n*)	Crude OR	95% CI	*P*	Adjusted OR[a]	95% CI[a]	Adjusted *P* value[a]
Non-Hispanic		347	141	—	—	—	—	—	—
	Vaginal	261	103	referent	—	—	referent	—	—
	Cesarean section	86	38	1.12	0.72–1.75	0.65	1.14	0.72–1.79	0.56
	Income	—	—	—	—	—	0.83	0.73–0.95	0.005
	Gestational age	—	—	—	—	—	1	0.92–1.11	0.87
	Breastfeeding	—	—	—	—	—	1.23	0.64–2.51	0.54
Hispanic		231	101	—	—	—	—	—	—
	Vaginal	194	76	referent	-	—	referent	—	—
	Cesarean section	37	25	1.73	0.97–3.06	0.07	2.34	1.23–4.46	0.009
	Income	—	—	—	—	—	0.69	0.58–0.81	<0.001
	Gestational age	—	—	—	—	—	1.11	0.99–1.13	0.07
	Breastfeeding	—	—	—	—	—	1.06	0.53–2.24	0.86

[a]All models adjusted for matching factors: age, sex, maternal race, and income.

a 22% increase in overall asthma risk in children delivered by CS (29). Similarly, type I diabetes risk is increased 23% following CS birth (30). Celiac disease and other immunoglobulin E-mediated food allergies have also been associated with CS, though more studies are needed for confirmation (31, 32). Associations between CS and intestinal bacterial infections have been identified in young children (33). CS may be an important factor in childhood leukemia through exposure to potentially pathogenic agents or human commensal organisms capable of modulating immune response across the life course (34).

There are many limitations in our study that limit a strong statistical inference of causality in the association of CS with ALL. We do not have data on elective versus emergency CS delivery; this may be an important factor in elucidating the mechanism of the association. Although CS is usually recalled correctly in questionnaires, in this study CS was recorded from birth certificates, in which any potential bias of questionnaire-derived exposure histories is deleted. Nevertheless, Hispanic status and other covariates are subject to potential misclassification biases. Although we believe misclassification of Hispanic status would be equal between groups, i.e., nondifferential, the possibility of differential misclassification remains. Although we control for socioeconomic status (SES) in our analyses the potential for unmeasured confounding influencing our measures of effect still remains. The cases are generally of a lower SES than our control subjects due to a lower response rate for controls versus cases. Although it is impossible to fully control for the potential influence of this SES difference, our findings, after adjusting for income in the analysis, combined with the similar findings of the previous Minnesota cohort study that was presumably not subject to this type of selection bias, suggest that the association we observed is indeed real. Whether these observed differences are the result of some unmeasured confounding or bias cannot be ascertained with these data. Replication of this association in other cohort studies will address the question more definitively.

The role of the primary population event of the infant microbiome in childhood leukemia remains unclear, but the data presented here suggest an etiologic function associated with early population of the human microbiome from the vaginal canal of the mother and raise many questions. Are there differences in elective versus emergency CS? Are certain cytogenetic subgroups affected disproportionately? What differences in colonization are associated with ALL? Does the initial immune function of the child affect future challenges by infectious agents? Does initial colonization create an ecologic dominance that modifies microbial competition? Are other social and environmental factors related to mode of delivery important?

If these results are replicated, it is possible that reduction of elective CS deliveries or CS delivery combined with alternative methods for microbial colonization of the neonatal gut may play a role in prevention of childhood leukemia. CS deliveries increased 56% in the United States from 1997 to 2006 rising to a rate of 32% of all births in 2006 (35). The majority of CS deliveries are elective. Additional research comparing the microbiome between children who develop leukemia and healthy children will aid in reconstructing the etiologic nature of this association. Those studies combined with epidemiologic evidence and immune profiling will help to shed further light on the etiology of this most common childhood cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the article. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIEHS.

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