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Infant leukemia and congenital abnormalities: A Children's Oncology Group study

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Abstract

Background—Leukemia in infants is rare and has not been well-studied apart from leukemia in older children. Differences in survival and the molecular characteristics of leukemia in infants vs. older children suggest a distinct etiology, likely involving prenatal factors.

Procedure—We examined the association between eight categories of maternally-reported congenital abnormalities (CAs) (cleft lip or palate, spina bifida or other spinal defect, large or multiple birthmarks, other chromosomal abnormalities, small head or microcephaly, rib abnormalities, urogenital abnormalities, and other) and infant leukemia in a case-control study. The study included 443 cases diagnosed at <1 year of age at a Children's Oncology Group institution in the United States or Canada from 1996-2006 and 324 controls. Controls were recruited from the cases' geographic area either by random digit dialing (1999-2002) or through birth certificates (2003-2008) and were frequency-matched to cases on birth year. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by unconditional logistic regression after adjustment for birth year and a measure of follow-up time to account for differences in the CA observation period.

Results—No statistically significant associations were observed between infant leukemia and any CA (OR=1.2; 95% CI 0.8-1.9), birthmarks (OR=1.4, 95% CI 0.7-2.5), urogenital abnormalities (OR=0.7; 95% CI 0.2-2.0), or other CA (OR=1.4; 95% CI 0.7-2.8). Results were similar for acute lymphoblastic and myeloid leukemia cases. Fewer than five subjects were in the remaining CA categories precluding analysis.

Conclusions—Overall, we did not find evidence to support an association between CAs and infant leukemia.

Keywords

infant leukemia; risk factors; congenital abnormalities; birth defects

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Introduction

Leukemia in infants is rare with an annual incidence rate of ~40 cases per million children <1 year of age in the United States [1]. Infant leukemia differs from that of older children in several respects including a lower five year survival rate of (~50% vs. 67-87%) [2] and translocations involving the mixed lineage leukemia (*MLL*) gene in a majority of cases [3,4]. These observations suggest that the etiology of infant leukemia is distinct from leukemias arising in older children.

Congenital abnormalities (CAs) and chromosomal syndromes have frequently been associated with childhood cancers and leukemia in particular. Most notably, Down syndrome is firmly established as a risk factor for leukemia [5] and several studies have suggested that CAs may be linked to leukemia including cleft lip/palate [6], rib abnormalities [7-10], other chromosomal abnormalities [11], pancreas-digestive tract abnormalities [12], large or multiple birthmarks [12], and heart defects [12,13]. Results of one study suggest that children born with CAs are more likely to be diagnosed with cancer during infancy than those without a CA [11]. The association between CAs and leukemia in infants, however, has not been specifically evaluated.

Using data from a Children's Oncology Group (COG) case-control study, we examined the association between infant leukemia and maternally-reported CAs. Results from this study may give insights into its pathogenesis.

Methods

Institutional Review Boards at the University of Minnesota and each case's COG institution approved the study protocol. Details of the case-control study design and data collection have been previously described [14-16] and are summarized below.

This study was conducted in two phases. Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) cases diagnosed from birth to age one year during 1/1/96-10/13/02 (phase one) and 1/1/03-12/31/06 (phase two) were identified through participating COG institutions in the United States and Canada. Subjects were excluded from the study if they had Down syndrome, their mother did not speak English or Spanish (Spanish language included in phase two only), or if their biological mother was not available for a telephone interview. Leukemia subtype and *MLL*-rearrangement status were verified as previously described [15,16].

Two hundred forty of 348 potential phase one cases completed interviews for a response rate of 69% as previously reported [16]. For phase two, 240 of 345 potential cases that were identified through 133 participating COG institutions were enrolled on study. Two hundred three (59%) mothers completed interviews, while the remainder did not due to maternal refusal (22%), inability to locate mother (11%), physician refusal (6%), and institutional failure to approach mother during study period (2%). Phase one controls (5/1999-10/2002) were sampled from the population through random digit dialing according to the procedure of Waksberg [17] with minor modifications and were frequency matched to cases on birth year. The field response rate of 59% for phase one controls was calculated according to the method by Slattery et al. [18] as previously detailed [14,16]. Phase two controls (10/2003-3/2008) were ascertained through state birth registries. Sixteen states were initially selected for control recruitment because of their ability to release birth records and because a substantial number of phase one cases were diagnosed in these states; 15 of these approved this study and provided lists of potential controls randomly selected from their birth registries. Controls were frequency matched to cases on birth year and region of residence based on the phase one case distribution with a recruitment goal of 150 additional controls.

Two-hundred seventy potential controls were approached with a mailed letter, of which 150 were located. Of these, 21 passively refused, 55 actively refused, and 3 were ineligible resulting in 71 completed interviews giving an overall response rate of 26%. Phase one and two controls were similar to one another based on maternal and infant characteristics as previously reported [14] and thus were combined as one control group.

Information on infant birth characteristics and maternal characteristics was collected through a structured telephone interview. Covariates considered in this analysis included infant sex, birth weight, gestational age, parental age, parental education, parental race, and annual household income. Information on the presence of Down syndrome and eight CA categories (cleft lip or palate; spina bifida or other spinal defect; large or multiple birthmarks; other chromosomal abnormalities; unusually small head or microcephaly; rib abnormalities; any kidney, bladder or sex organ abnormalities (urogenital abnormality); any other birth defect) in case and control subjects and their siblings was collected during the mother's telephone interview. If mothers reported an 'other' CA in their offspring, they were asked to specify the type.

Statistical analyses

All statistical analyses were conducted using SAS version 9.1 (Cary, NC). Statistical differences in the frequency or means of sociodemographic and infant characteristics between cases and controls were assessed using Fisher's exact test and one-way analysis of variance for categorical and continuous variables respectively. We used unconditional logistic regression to examine associations between infant leukemia and CAs in index children and their siblings after adjusting for birth year. Since some CAs are not readily observed until after the first year [19], we also adjusted for a measure of follow-up time in models for associations between CAs and infant leukemia in index children. Follow-up time was defined as the interval between the birth date and interview or death date, whichever came first and was dichotomized at the median (based on both case and control subjects). Potential confounders of the association between CAs and infant leukemia overall were examined using a forward selection process [20] where each potential confounder was added one at a time to models that included birth year to determine their effect on the parameter estimate. If a potential confounder materially changed the interpretation of the result, it was retained in the model. All statistical tests were two-sided.

Results

Approximately 60% and 39% of infant cases had a diagnosis of ALL or AML, respectively, with the remaining cases having diagnoses of biphenotypic or acute unknown leukemias. Among cases with known *MLL*-rearrangement status, over half were *MLL*-positive with a ratios of ~2:1 and 1:1 for ALL and AML *MLL*-positive to negative cases respectively. The mean diagnosis age was ~6 months overall with *MLL*-positive cases tending to be diagnosed earlier than other cases. There were more females than males among *MLL*-positive cases with the reverse finding among *MLL*-negative and unknown cases (Table I).

The mean gestational age and birth weight was similar between cases and controls, while cases were more likely than controls to be first born (Table II). Case mothers were slightly younger, and more likely to report household incomes of $\leq \$30,000$, being unmarried, and non-White. Notably, over twice as many case than control mothers reported being of Hispanic ethnicity. A similar percentage of case and control mothers reported having college degrees.

Logistic regression results for associations between infant leukemia and CAs with ≥ 5 case and control subjects in index children are provided in Table III. There were no significant

associations between infant leukemia overall and any CA (OR=1.2; 95% CI 0.8-1.9), large or multiple birthmarks (OR=1.3; 95% CI 0.7-2.4), urogenital system abnormalities (OR=0.7; 95% CI 0.2-2.0), or other CAs (OR=1.4; 95% CI 0.7-2.8) in models that adjusted for birth year and follow-up time category or in those that also included other covariates shown in Table II (data not shown). Results were similar when analyzed for ALL and AML infant leukemia subtypes specifically. We observed no significant effect modification by sex with the exception of a marginally significant interaction (p for interaction=0.1) between large or multiple birthmarks and infant leukemia overall (OR_{males}=0.7; 95% CI 0.3-1.8; OR_{females}=2.1; 95% CI 0.9-5.1). Risks of similar magnitude in association with birthmarks were apparent in females for ALL (OR=2.4; 95% CI 0.9-6.4) and AML (OR=2.7; 95% CI 0.9-7.9) (Supplementary Tables I-III).

We examined whether associations between infant leukemia and CAs varied by *MLL*-rearrangement status. *MLL*-positive cases had nonsignificant increased risks of leukemia in association with birthmarks (OR=1.5, 95% CI 0.7-3.2) and other CAs (OR=2.0, 95% CI 0.9-4.5) (Supplementary Table IV). Similar percentages of ALL and AML *MLL*-positive cases had reported birthmarks (10.2% and 11.8% respectively). We found significant effect modification by sex of the association between birthmarks but not other CAs and *MLL*-positive leukemia (p for interaction=0.05) with an increased risk in females (OR_{females}=2.9; 95% CI 1.0-7.9) but not males (OR_{males}=0.7; 95% CI 0.2-2.1) (Supplementary Table V).

Finally, we examined whether CAs in the siblings were associated with infant leukemia. No significant associations were found between sibling CAs and infant leukemia for any CA (OR=1.1; 95% CI 0.7-1.6), large or multiple birthmarks (OR=0.9; 95% CI 0.5-1.7), urogenital system abnormalities (OR=1.2; 95% CI 0.4-3.1), or other CA (OR=1.0; 95% CI 0.5-1.9) (Supplementary Table VI).

Discussion

In this study, we did not find statistical evidence for an association between maternally-reported CAs and infant leukemia. Previous studies have suggested that several types of CAs confer an increased risk for leukemia. However, not all previous studies have excluded individuals with Down syndrome from their analyses [11,21]. In studies that have excluded these individuals, non-significant associations have generally been reported between leukemia (AML, ALL, or total) and any congenital anomaly [13,22-29], major congenital anomalies [30], and heart defects [13,22], while significant associations have been reported for birthmarks (ALL and AML) [12,31], heart abnormalities (ALL) [12], and pancreas or digestive tract abnormalities (ALL) [12]. Our finding of no overall association between CAs and infant leukemia is consistent with that of most previous studies that have excluded Down syndrome.

Our finding of a twofold increase risk of infant leukemia in association with large or multiple birthmarks in females is intriguing in light of reports by four previous studies (two of childhood cancer and two of childhood leukemia) that have reported significant positive associations for birthmarks [12,31-33]. Mertens et al. [12] reported significant increased risks for large or multiple birthmarks overall in the index child but not their siblings for both ALL (OR=1.3; 95% CI 1.1-1.7) and AML (OR=1.9; 95% CI 1.2-3.1). Roganovic et al. [31] reported significant excesses of pigmented nevi and café-au-lait spots in children with hematological malignancies, while Johnson et al. [32] and Merks et al. [33] reported increased frequencies of birthmarks and port-wine stains respectively in childhood cancer cases compared to non-cases. Similar to the results of our study, Johnson et al. [32] also reported a female excess in cases with birthmarks. A biological explanation for these findings is unclear as none of these studies have included cases that were reported to have

neurofibromatosis type 1 that is characterized by the presence of café-au-lait spots and an increased risk of leukemia [3].

Intriguingly, four studies have reported significant positive associations between rib abnormalities and leukemia [7-10]. However, only two of these studies reported excluding children with Down syndrome, which has previously been noted to be associated with an excess of rib abnormalities [34]. Two controls and no cases had reported rib abnormalities in our study, a lower than expected frequency [8-10], that is likely due to under-reporting since mothers may not be aware of rib abnormalities in the absence of their child having undergone a chest X-ray.

One previous study has suggested that children born with a CA are at greater risk for cancer in the first year of life than children born without a CA [11] implicating the infant period as being the most vulnerable to development of malignancy. The risk for leukemia was mainly due to chromosomal anomalies (including Down syndrome) and not other defects, which is consistent with our findings.

This study has strengths and limitations. Our study is the largest study to date to examine risk factors for infant leukemia specifically, and included a nearly population-based source of cases diagnosed in the United States and Canada through the COG [35,36]. In addition, all data were collected systematically by trained interviewers. A limitation of our study is that CAs were ascertained by maternal interview, which may miss CAs that are minor or not clearly visible. We were also limited by low statistical power to detect modest effect sizes. For example, we had 80% power to detect an increased OR of 1.7 for the overall association between CAs and infant leukemia. Recall or reporting bias could have affected our results if the maternal reporting accuracy of CAs varied by cancer status. Positive bias could result if mothers over-reported CAs in case children. However, this seems unlikely to have occurred since associations between sibling CAs and infant leukemia were near unity. Selection bias may also have affected our results since our controls were different on several respects from cases and the general population as previously reported [14]. However, adjustment for factors that differed between cases and controls did not materially change the results.

In conclusion, this study does not provide evidence for a strong association between CAs and infant leukemia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table I

Characteristics of infant leukemia diagnoses

	<i>MLL</i> -positive (n=228)	<i>MLL</i> -negative (n=146)	<i>MLL</i> -unknown (n=69)	Total (n=443)
Leukemia subtype; No. (%)				
ALL	157 (69)	77 (53)	30 (43)	264 (60)
AML	68 (30)	66 (45)	38 (55)	172 (39)
other	3 (1)	3 (2)	1 (2)	7 (2)
Diagnosis age category; No. (%)				
< 6 months	134 (59)	63 (43)	28 (41)	225 (51)
≥ 6 months	94 (31)	83 (57)	41 (59)	218 (49)
Mean (SD)	5.7 (3.1)	6.8 (3.5)	6.8 (3.5)	6.2 (3.4)
Gender; No. (%)				
Male	103 (45)	77 (53)	38 (55)	218 (49)
Female	125 (55)	69 (47)	31 (45)	225 (51)

Table II

Birth characteristics and parental sociodemographics of cases and controls

Characteristic	Controls	Cases	p-value ^a
Gestational age category; No. (%)			
< 37 weeks	24 (7.4)	32 (7.2)	
37 - 42 weeks	299 (92.3)	410 (92.6)	
> 42 weeks	1 (0.3)	1 (0.2)	1.0
Mean (sd)	39.3 (1.9)	39.2 (1.8)	
Birth weight category (grams); No. (%)			
<1500	4 (1.23)	3 (0.7)	
1500-2499	13 (4.0)	20 (4.5)	
2500-3999	258 (79.6)	351 (79.2)	
≥4000	49 (15.1)	69 (15.6)	0.86
Mean (sd)	3436.3 (591.8)	3477.3 (572.4)	
First-born; No. (%)			
no	206 (63.6)	253 (57.1)	
yes	118 (36.4)	190 (42.9)	0.07
Maternal age category; No. (%)			
≤24 years	43 (13.3)	100 (22.6)	
25-29 years	128 (39.6)	138 (31.2)	
30-34 years	94 (29.1)	134 (30.3)	
≥35 years	58 (18.0)	70 (15.8)	0.004
Mean (sd)	29.8 (5.4)	29.1 (5.7)	
Household income category (US dollars)^b ; No. (%)			
≤30,000	95 (29.6)	157 (35.8)	
30,001-75,000	145 (45.2)	189 (43.1)	
>75,000	81 (25.2)	93 (21.2)	0.16
Marital status; No. (%)			
Married	274 (84.6)	350 (79.0)	
Unmarried	50 (15.4)	93 (21.0)	0.05
Maternal Race; No. (%)			
White, not of Hispanic origin	273 (84.5)	334 (75.6)	
African-American or Black, not of Hispanic origin	18 (5.6)	18 (4.1)	
Hispanic	15 (4.6)	55 (12.4)	
Native American Indian or Alaskan Native	4 (1.2)	9 (2.0)	
Asian, Asian-American, or Pacific Islander	8 (2.5)	22 (5.0)	
Other	5 (1.6)	4 (0.9)	<0.001
Maternal Education^c ; No. (%)			
≤High school	91 (28.2)	149 (33.7)	
Some college	112 (34.7)	125 (28.3)	
College graduate	120 (37.2)	168 (38.0)	0.12

^a p-values calculated by Fisher's exact test

^b 3 cases and 4 controls had missing data on household income

^c 1 case and 1 control had missing data on maternal education

Table III

Associations between infant leukemia and maternally-reported congenital abnormalities overall and by leukemia subtype

Congenital abnormality category	Total				ALL				AML				
	Controls (no.)	Cases (no.)	OR ^c	95% CI	Cases (no.)	OR ^c	95% CI	Cases (no.)	OR ^c	95% CI	Cases (no.)	OR ^c	95% CI
Any													
no	284	366	1	ref.	217	1	ref.	142	1	ref.	142	1	ref.
yes	40	77	1.2	0.8-1.9	47	1.4	0.8-2.3	30	1.4	0.8-2.4	30	1.4	0.8-2.4
Large or multiple birthmarks													
no	306	402	1	ref.	238	1	ref.	157	1	ref.	157	1	ref.
yes	18	41	1.3	0.7-2.4	26	1.5	0.8-3.0	15	1.4	0.6-2.9	15	1.4	0.6-2.9
Urogenital system abnormality													
no	315	434	1	ref.	259	1	ref.	168	1	ref.	168	1	ref.
yes	9	9	0.7	0.2-2.0	5	0.8	0.2-2.6	4	0.7	0.2-3.2	4	0.7	0.2-3.2
Other													
no	308	414	1	ref.	247	1	ref.	160	1	ref.	160	1	ref.
yes	15	29	1.4	0.7-2.8	17	1.5	0.7-3.3	12	1.6	0.7-3.8	12	1.6	0.7-3.8

^a Adjusted for birth year and follow-up time category dichotomized at the median (27, 32, and 34 months for total, AML, and ALL analyses respectively)