Evaluating the Role of Birth Weight and Gestational Age on Acute Lymphoblastic Leukemia Risk among Those of Hispanic Ethnicity

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ABSTRACT

High birth weight is an established risk factor for childhood acute lymphoblastic leukemia (ALL), especially in children younger than 5 years of age at diagnosis. The goal of this study was to explore the association between being born large for gestational age and the risk for ALL by race/ethnicity to determine if the role of this risk factor differed by these characteristics. The authors compared birth certificate data of 575 children diagnosed with ALL who were younger than 5 years and included in the Texas Cancer Registry, Texas Department of Health, between the years 1995 and 2003 with 11,379 controls matched by birth year. Stratified odds ratios were calculated for risk of ALL by birth weight for gestational age, categorized in 3 groups, small, appropriate, and large for gestational age (SGA, AGA, LGA, respectively), for each race/ethnicity group. The risk of developing ALL was higher among Hispanics who were LGA (odds ratio [OR]= 1.90, 95% confidence interval [CI]: 1.34-2.68) compared with LGA non-Hispanic whites (OR= 1.27, 95% CI: 0.87-1.86) after adjusting for infant gender, year of birth, maternal age, birth order, and presence of Down syndrome. However, the difference was not statistically significant. These results suggest that there may be differences in the association between higher growth in utero and risk of childhood ALL among Hispanics versus non-Hispanic whites.

INTRODUCTION

Acute lymphoblastic leukemia (ALL), the most common pediatric malignancy, represents about 25% of childhood cancers among those younger than 20 years of age, with approximately 4900 new cases diagnosed annually in the United States.[1] Approximately 5% of cases are attributable to a genetic condition,[2] exposure to radiation,[3,4] or previous chemotherapy treatment.[5] However, most cases are of unknown etiology. In spite of this, some risk factors have been consistently associated with ALL. For instance, males have a higher incidence of ALL compared to females, and Hispanics (i.e., those from Spanish-speaking countries, especially those of Latin America) have a higher incidence compared with other racial/ethnic categories.[6,7] Additionally, high birth weight (HBW) is an established risk factor for the development of ALL.[8,9]

The mechanism underlying the association between HBW and ALL remains unclear; therefore, it is important to better characterize this relationship. For instance, birth weight corrected for gestational age (BWGA) is a better measure for ALL risk than HBW alone.[10-13] Specifically, in our own assessment using a large population-based sample from Texas, we demonstrated that large for gestational age (LGA) categories yielded more precise estimates of the association between birth weight and ALL compared to birth weight categories.[10] Although there are differences in risk of ALL between Hispanics and non-Hispanic whites there are also differences between these groups on mean birth weight and preterm birth rate.[14,15] In spite of this, ethnic differences have not been fully explored in the context the association between LGA and ALL risk.

As the incidence of ALL is higher among Hispanics compared with non-Hispanic whites, there is a need to better distinguish risk factors among this population. Therefore, the objective of this study was to evaluate the association between birth weight corrected for gestational age BWGA and ALL among Hispanics and compare those findings with those among non-Hispanic whites. This population-based case-control study from the Texas Cancer Registry identified 575 childhood ALL cases and 11,379 controls is one of the largest of its kind.

MATERIALS AND METHODS

Selection of Cases and Controls

This study was approved by the Texas Cancer Registry (TCR) institutional review board (IRB) for use of its data; the Texas Department of State Health Services (DSHS) IRB for use of birth records from the Bureau of Vital Statistics; and the Baylor College of Medicine IRB. Details of study design and methods have been described elsewhere.[10] In brief, birth certificate data were collected from all children who were singleton births in Texas, aged less than five years, diagnosed with a malignancy between 1995 and 2003, and registered by the TCR of the DSHS (N=3450). TCR data were linked to birth certificate data using a probabilistic linkage software program AUTOMATCH Generalized Record Linkage System software (Match Ware Technologies, Silver Spring, MD, 1992); and 2673 of the initially identified 3450 total cases (77%) were successfully matched to their birth records. The control subjects were drawn from residual (i.e., not matched to TCR) Texas birth files for the study period and frequency-matched at a 5:1 ratio to all cancer cases on birth year only. Cases and controls were excluded if gestational age (GA) and/or BW were missing or if BW was less than 500 g. Specifically, 11.6% of cases versus 12.4% of controls were missing information on GA and/or BW. After these exclusions, there were a total of 575 ALL cases and 11,379 control subjects available for analysis.

Data abstraction

Details of data abstraction have been described elsewhere.[10] Briefly, we extracted data from the birth certificate files for variables previously associated with

childhood cancer or plausibly associated with BW, GA, or childhood cancer. The variables abstracted and used in the analyses included: infant gender, race/ethnicity (recorded as the race of the mother on the birth certificate in The State of Texas), birth order, maternal age, paternal age, GA (in weeks), BW (in grams), and having a congenital malformation or Down syndrome. BW and GA were used to calculate BWGA. Specifically, race- and gender-specific growth curve data[16] were used to categorize each subject's weight corrected-for-gestational age as small for GA (SGA), appropriate for GA (AGA), or LGA. The LGA category included children whose weight at the given GA was greater than the 90th percentile; the SGA category included children whose weight at each GA in weeks was below the 10th percentile.

Statistical analysis

Counts and proportions were used to evaluate differences between ALL cases and controls on the variables included in the analysis. We conducted unconditional logistic regression analysis to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to determine the crude association between selected characteristics and ALL, stratified by race/ethnicity. In order to evaluate the adjusted association between BWGA and ALL, we used multivariable logistic regression, evaluating the following factors as potential confounders: infant gender (male or female), maternal age (<20, 20-24, 25-29, 30-34, ≥35), paternal age (<20, 20-24, 25-29, 30-34, ≥35), birth order (1, 2, ≥3), congenital malformation (yes or no), and Down syndrome (yes or no).[10,17] As cases and controls were frequency-matched on year of birth, all models were adjusted for this variable. In addition based on previous studies, we opted to include infant gender, birth order, maternal age, and presence of Down syndrome in all models.[10] Finally, in order

to determine if there were differences between non-Hispanic whites and Hispanics for the risk of ALL by BWGA, we conducted the Breslow-Day test of homogeneity. All statistical tests were 2-sided and performed with Stata software, version 13 (College Station, TX). We considered a 2-sided *P* value of <.05 as statistically significant.

RESULTS

Complete epidemiologic data were available on 575 ALL cases and 11,379 controls subjects. Birth characteristics are summarized in Table 1. Cases were more likely to be Hispanic or non-Hispanic white compared with controls (48.4% vs. 45.9% and 47.1% vs. 42.3%, respectively). Compared to controls, cases were more likely to be male (55.8% vs. 50.8%), born to mothers ≥30 years of age (31.7% vs. 28.2%), born to fathers ≥30 years of age (43.1% vs. 36.7%), LGA (14.1% vs. 9.8%), have a BW ≥4000 grams (15.0% vs. 10.4%), born with a congenital malformation (1.4% vs. 0.8%), and have Down syndrome (0.7% vs. 0.04%).

Unadjusted associations between selected variables and ALL by race/ethnicity are presented in Table 2. Among non-Hispanic whites, there were significant associations between ALL and the following: maternal age (odds ratio $[OR]_{(25\text{-}29)}$= 1.88, 95% confidence interval [CI]: 1.11-3.19; $OR_{(30\text{-}34)}$= 1.98, 95% CI: 1.16-3.39; $OR_{(\geq 35)}$= 1.89, 95% CI: 1.05-3.40), having been born with congenital malformation (OR= 2.60, 95% CI: 1.09-6.17), and having Down syndrome (OR= 17.99, 95% CI: 4.48-72.34). We also observed significant associations between ALL and being LGA (OR= 1.73, 95% CI: 1.23-2.43), and having birth weight ≥4000 grams (OR= 1.70, 95% CI: 1.19-2.42) among Hispanics. None of the variables evaluated were significantly associated with ALL among non-Hispanic blacks.

The risk of developing ALL was higher among Hispanics who were LGA (OR= 1.90, 95% CI: 1.34-2.68) compared with LGA non-Hispanic whites (OR= 1.27, 95% CI: 0.87-1.86) after adjusting for infant gender, year of birth, maternal age, birth order, and presence of Down syndrome (Table 3). Although LGA-associated ALL risk was higher in

Hispanics compared with non-Hispanic whites, the Breslow-Day test of homogeneity was $P = .22$.

DISCUSSION

In one of the largest assessments of its kind, we assessed the differences between Hispanics and non-Hispanic whites on association between BWGA and ALL. Although the risk of ALL due to being LGA was about 50% higher among Hispanics when compared with non-Hispanic whites, the difference was not statistically significant.

Other assessments have noted differences in the risk of ALL between Hispanics and non-Hispanic whites.[18,19] In a Spanish population with ALL, García-Sanz et al.- observed an absence of TEL- AML1 gene translocation and suggested the presence of racial variation in terms of underlying etiology.[19] This hypothesis was confirmed by another study in the United States population comparing Hispanics and non-Hispanic whites in California. Briefly, the percentage of TEL-AML1 gene translocation was significantly lower in Hispanics compared with non-Hispanic whites (P = .01).[18] In addition, in one case-control study, Xu et al.[20] evaluated the frequency of 49 *ARID5B* single-nucleotide polymorphisms and observed that the frequency of the ALL risk alleles (allele C) was higher in Hispanics compared with non-Hispanic whites. The authors concluded that *ARID5B* polymorphisms may contribute to racial disparities in the incidence of childhood ALL. Furthermore, Kennedy et al. reported differences in genetic associations with the risk of childhood ALL between Hispanics and non-Hispanics whites.[21,22] Therefore, previous assessments suggest the risk factor profile may differ between Hispanics and other groups.

Although HBW is a well-established risk factor for development of childhood ALL,[8,9] the biological mechanism underlying this association remains unclear.

Furthermore, differential effects of HBW across race and ethnicity groups have not been extensively evaluated. The association of BW and the risk of childhood cancer by race/ethnicity was previously studied by Okcu et al.[23] Unlike the present study, the authors studied BW alone instead of BWGA, which we believe is a better predictor for occurrence of ALL in children.[10] They showed that the variable of race/ethnicity did not influence the association between BW and childhood ALL.[23] Unlike the previous study, the association between LGA and ALL was about 50% stronger among Hispanics when compared with non-Hispanic whites.

Our findings must be considered in the light of certain limitations. For instance, using GA to define risk group limited the number of potential cases and controls available for analysis. Additionally, some subjects were missing information on GA and/or BW. However, proportions were similar between cases and controls, which limits the possibility of selection bias. The data for the GA may not be recorded properly in birth certificates, which can lead to exposure misclassification bias by incorrectly categorizing subjects with respect to their BWGA. As this is not likely to vary by case status, we believe the potential for misclassification would be nondifferential, leading to our effect estimates being biased towards the null.[24] Additionally, use of maternal self-reported race and ethnicity may introduce some heterogeneity. Third, the study population is limited to those who were born and diagnosed in Texas, therefore, children who moved out of the state prior to diagnosis or children not born in Texas could not be included in this assessment. A final limitation of this study is that 23% of the cases were not linked to birth records. This is likely due to cases diagnosed in Texas who were not born in the state. It should also be noted that some children born in Texas might be

diagnosed with cancer in other states and not ascertained by the Texas Cancer Registry. Although it is difficult to determine the direction in which this may bias our results, we believe movement between cases and controls is likely nondifferential.[25] Therefore, we believe our effect estimates would be biased toward the null based on this limitation.[24]

Strengths of this study include a large sample size. In addition, we used a growth curve data provided by Alexander[16] to assess neonatal growth and BWGA, which we previously showed is a better measurement in defining standardized risk groups than BW alone.[10] Finally, we utilized data from a large population-based cancer registry that enabled us to evaluate the role of BWGA on ALL risk among Hispanics.

In summary, despite some important limitations, we found a somewhat stronger association between high BWGA and ALL among Hispanics compared with non-Hispanic whites. This information supports the etiologic underpinnings of ALL may be different in Hispanics compared with other groups. We recommend that future research would benefit from defining Hispanic ethnicity based on genomic ancestry. Additionally, characterizing the biological mechanism underlying the association between BWGA and childhood ALL may be informative for future prevention strategies.

Table 1. Characteristics of ALL cases and controls in Texas, 1995-2003

Variable	ALL cases (N=575)		Controls (N=11,379)	
Gender, n (%)				
Female	254	(44.2)	5,598	(49.2)
Male	321	(55.8)	5,781	(50.8)
Race/ethnicity,[a] n (%)				
Non-Hispanic white	271	(47.1)	4,808	(42.3)
Non-Hispanic black	26	(4.5)	1,346	(11.8)
Hispanic	278	(48.4)	5,225	(45.9)
Maternal Age (years), n (%)				
Mean (SD)	26.6	(6.0)	25.9	(6.0)
<20	69	(12.0)	1,823	(16.0)
20-24	153	(26.6)	3,286	(28.9)
25-29	171	(29.7)	3,071	(27.0)
30-34	124	(21.6)	2,147	(18.9)
≥35	58	(10.1)	1,052	(9.3)
Paternal Age (years), n (%)				
Mean (SD)	29.8	(6.9)	28.9	(6.8)
<20	26	(4.5)	528	(5.1)
20-24	95	(16.5)	2,170	(19.1)
25-29	135	(23.5)	2,721	(23.9)
30-34	123	(21.4)	2,301	(20.2)
≥35	125	(21.7)	1,872	(16.5)
Missing	71	(12.4)	1,733	(15.2)
Gestational age (weeks)				
< 37	56	(9.7)	1,104	(9.7)
37-40	459	(79.8)	8,982	(78.9)
≥41	60	(10.4)	1,293	(11.4)
Weight corrected for gestational age				
SGA	48	(8.3)	1,219	(10.7)
AGA	446	(77.6)	9,040	(79.4)
LGA	81	(14.1)	1,120	(9.8)
Birth weight (g)				
≤2,500	26	(4.5)	642	(5.6)
2,501-3,999	463	(80.5)	9,557	(84.0)
≥4,000	86	(15.0)	1,180	(10.4)
Birth Order				
1	235	(42.65)	4,520	(41.16)
2	166	(30.13)	3,355	(30.55)
≥3	150	(27.22)	3,106	(28.29)
Congenital malformation				
No	555	(96.5)	11,136	(97.9)
Yes	8	(1.4)	92	(0.8)
Missing	12	(2.1)	151	(1.3)
Down syndrome				

No	571	(99.3)	11,374	(99.96)
Yes	4	(0.7)	5	(0.04)

Note. SD= standard deviation

[a]Recorded on birth certificates as the race of the mother for controls;.

Table 2. Associations between birth characteristics and ALL by race/ethnicity in Texas, 1995-2003

	Non-Hispanic Whites Cases/controls (271/4,808)		Non-Hispanic Blacks Cases/controls (26/1,346)		Hispanics Cases/controls (278/5,225)	
Variable	OR	95% CI	OR	95% CI	OR	95% CI
Gender						
Female	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
Male	1.21	(0.94-1.54)	1.72	(0.76-3.89)	1.22	(0.96-1.55)
Maternal Age (years)						
<20	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
20-24	1.49	(0.86-2.58)	0.75	(0.24-2.34)	1.14	(0.79-1.65)
25-29	1.88	(1.11-3.19)	1.32	(0.44-3.98)	1.20	(0.83-1.74)
30-34	1.98	(1.16-3.39)	1.16	(0.35-3.84)	1.24	(0.81-1.88)
≥35	1.89	(1.05-3.40)	1.01	(0.20-5.08)	1.17	(0.68-2.00)
Paternal Age (years)						
<20	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
20-24	0.78	(0.35-1.72)	0.60	(0.11-3.34)	1.15	(0.65-2.02)
25-29	1.03	(0.49-2.19)	0.31	(0.04-2.24)	1.18	(0.67-2.06)
30-34	1.15	(0.54-2.43)	0.72	(0.13-4.00)	1.16	(0.65-2.06)
≥35	1.38	(0.65-2.92)	1.00	(0.20-5.08)	1.56	(0.87-2.79)
Gestational age (weeks)						
< 37	1.23	(0.81-1.85)	0.22	(0.03-1.64)	1.03	(0.68-1.54)
37-40	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
≥41	0.76	(0.50-1.17)	0.62	(0.14-2.64)	1.08	(0.75-1.57)
Weight corrected for gestational age						
SGA	0.87	(0.56-1.34)	1.44	(0.49-4.28)	0.68	(0.43-1.08)
AGA	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
LGA	1.27	(0.88-1.84)	0.82	(0.19-3.55)	1.73	(1.23-2.43)
Birth weight (g)						
≤2,500	0.53	(0.25-1.15)	1.53	(0.52-4.55)	1.16	(0.68-1.99)
2,501-3,999	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
≥4,000	1.25	(0.90-1.74)	1.59	(0.36-6.93)	1.70	(1.19-2.42)
Birth Order						
1	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
2	1.00	(0.76-1.33)	0.62	(0.23-1.64)	0.92	(0.67-1.26)
≥3	0.91	(0.66-1.25)	0.70	(0.28-1.77)	1.00	(0.75-1.35)
Congenital malformation						
No	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
Yes	2.60	(1.09-6.17)	N/A[a]	N/A	1.08	(0.26-4.51)
Down syndrome						
No	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
Yes	17.99	(4.48-72.34)	N/A[a]	N/A	N/Aa	N/A

Note. SGA=Small for Gestational Age; AGA=Average for Gestational Age; LGA=Large for Gestational Age;
[a]Some cells have zero observation.

Table 3. Risk of ALL by birth weight corrected for gestational age by ethnicity in Texas, 1995-2003

Weight corrected for gestational age	Adjusted[a] OR (95% CI) Non-Hispanic white	Adjusted[a] OR (95% CI) Hispanic	*P* for Heterogeneity
SGA	0.90 (0.58-1.40)	0.76 (0.47-1.22)	.22
AGA	1.00 (Ref.)	1.00 (Ref.)	
LGA	1.27 (0.87-1.86)	1.90 (1.34-2.68)	

*Note.*SGA=Small for Gestational Age; AGA=Average for Gestational Age; LGA=Large for Gestational Age.[a]Adjusted for infant gender, and maternal age.

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