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Immune-related conditions and acute leukemia in children with Down syndrome: A Children's Oncology Group report

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Abstract

Background—Children with Down syndrome (DS) have unique immune profiles and increased leukemia susceptibility.

Methods—Mothers of 158 children with DS diagnosed with acute leukemia at 0-19 years in 1997-2002 and 173 children with DS but no leukemia were interviewed. Associations were evaluated via multivariable unconditional logistic regression.

Results—No associations were detected for asthma, eczema, allergies, or hypothyroidism. Diabetes mellitus associated with leukemia (odds ratio=9.23, 95% confidence interval: 2.33-36.59), however most instances occurred concurrent with or after the leukemia diagnosis.

Conclusions and Impact—Children with DS who develop leukemia have increased diabetes risk, likely due to treatment and underlying susceptibility factors.

Keywords

epidemiology; children; Down syndrome; diabetes mellitus; leukemia

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Introduction

Children with Down syndrome (DS) have 10- to 45-fold greater risk for developing acute leukemia compared with the general population.(1, 2) The extra copy of chromosome 21 is thought to be an important contributing factor, however, the mechanism behind this higher susceptibility is not well characterized.(3)

Children with DS are also known to have immune system dysregulation. Abnormalities in cell proportions and absolute counts have been reported, including reduced pools of naïve B cells, CD4+ and CD8+ T lymphocytes, and NK cells, and increased numbers of proinflammatory $CD14_{dim}CD16+$ monocytes.(4) Differences in cytokine levels have also been observed.(5) For example, expression of interferon gamma, a cytokine central to the immune response to infectious pathogens and tumor cells, and its receptor IFNGR2, encoded on chromosome 21, are higher among children with DS.(6, 7) These differences correspond to an altered distribution of co-morbidities, where children with DS have increased rates of infections and autoimmunity (e.g., diabetes mellitus (DM), hypothyroidism), but develop atopy and asthma far less frequently than their euploid counterparts.(8, 9)

Several autoimmune diseases have been correlated with increased hematopoietic cancer risk.(10, 11) In children, strong associations have been reported between DM and acute lymphoblastic leukemia (ALL); however, DM often presents after the leukemia diagnosis and may be self-limiting.(12, 13) Notably, the development of transient DM in ∼10% of ALL patients during treatment with L-asparaginase and glucocorticoids has been well documented.(14, 15) Presenting symptoms include hyperglycemia and, in rarer cases, diabetic ketoacidosis.(14) The DM is managed by monitoring glucose levels, administration of IV fluids, dietary modifications, increased exercise, and administration of insulin as needed.(15) Children with DS are one of the groups at higher risk of transient DM.(14) In a series of 421 childhood ALL patients, host factors associated with treatment-related hyperglycemia included DS (RR=7.17), age ≥10 years (RR=6.68), and obesity (RR=8.53).(14) The DM often resolves after the discontinuation of the responsible therapeutic agent(s),(14, 15) however, ALL survivors are at increased risk for chronic DM following treatment.(16) To our knowledge, no prior studies have examined autoimmune diseases as risk factors for acute leukemia in children with DS.

There is ongoing debate regarding the nature of the association between atopic disease and childhood ALL, with most studies reporting inverse associations,(17) and other, record-base studies suggesting increased risks.(18, 19) Inverse associations with acute myeloid leukemia (AML) have also been observed for a smaller number of studies.(17) A recent case-control study in children with DS reported an increased odds of acute leukemia associated with asthma (OR=4.18, 95% CI: 1.47-11.87), and an inverse association with skin allergies (OR=0.42, 95% CI: 0.20-0.91).(20)

Here we tested the null hypothesis of no association between asthma, eczema, allergies, DM, or hypothyroidism in children with DS or their siblings, respectively, and acute leukemia.

Materials and Methods

Methods for this Children's Oncology Group (COG) study have been described elsewhere(21) and are summarized below. Eligible cases had a prior DS diagnosis, an acute leukemia diagnosis between 0-19 years of age in 1/1/1997-10/31/2002 at a U.S. or Canadian COG institution, a residential telephone line, and a consenting biological mother that spoke English. Deceased cases were eligible.

After completing telephone interviews, case mothers were asked to provide contact information for the index child's primary care provider. Controls were randomly selected from rosters of children with DS generated by the cases' providers. Like cases, control children with a prior diagnosis of DS (but no cancer diagnosis), residential telephone line, and consenting biological mother that spoke English were eligible. Controls were frequency matched to cases in the age groupings: 0, 1-3, 4-6, 7-10, 11-14, and 15-18 years. DS and leukemia diagnoses were confirmed by central pathology review. To ensure similar exposure time periods for questions regarding childhood exposures in cases and controls, controls were randomly assigned a reference date in the 6 months prior to their birthday in the calendar year assigned in the frequency matching process; the pseudo-diagnosis date corresponded to the date exactly 6 months after the reference date. Similarly, the reference date assigned to cases was the date 6 months prior to the leukemia diagnosis.

Data on prior diagnosis of asthma, eczema, allergies, DM, thyroid conditions, and covariates were ascertained by maternal telephone interviews (n_{cases}=158, $n_{controls}$=173). Because these conditions are known to cluster within families and have substantial genetic contributions to the observed heritability,(22, 23) multiparous mothers were also asked if their other children had been diagnosed with these conditions (n_{cases}=135, $n_{controls}$=152).

Institutional Review Boards of the University of Minnesota and participating COG institutions approved the study.

Statistical Analysis

We estimated associations between the specified conditions and acute leukemia, overall and for ALL and AML separately, via multivariable unconditional logistic regression (SAS 9.2, SAS Institute Inc., Cary, NC, USA); odds ratios (ORs) and 95% confidence intervals (CIs) were generated for two time periods, any time and 6 months or more prior to leukemia diagnosis (cases) or pseudo-diagnosis date (controls). Reference age, the frequency matching variable, was included in all models. Possible confounders listed in Table 1 were selected *a priori*; those that changed the ln(ORs) by ≥10% were retained in final models.

Results

In total, 210 eligible cases were identified at 116 North American COG institutions and 158 mothers completed interviews (97 ALL, 61 AML), for an overall response rate of 75%. Of the 215 mothers of eligible controls contacted, 173 participated (response rate=80.5%). Cases and controls were similar on several characteristics (Table 1), however, control

mothers tended to be slightly younger at the index child's birth, have higher educational attainment, and be non-Hispanic white compared with case mothers.

As shown in Tables 2 and 3, the adjusted logistic regression results provided little evidence for associations between immune-mediated conditions in index children or their siblings and development of acute leukemia, ALL, or AML. A notable exception was the strong positive association between DM in index children in any time period and acute leukemia overall (OR=9.23, 95% CI: 2.33-36.59); the estimate lacked precision, however, due to the limited number of affected subjects (15 cases, 3 controls). Because 14/15 cases (all of them with ALL) and 2/3 controls were diagnosed with DM <6 months preceding or after the leukemia diagnosis, the association was no longer observed in examining only DM diagnosed ≥6 months prior to leukemia (OR=0.92; CI: 0.05-15.41).

A sensitivity analysis restricting cases to those with a control from the same primary care clinic (n=67) produced similar results (data not shown), thereby minimizing concerns regarding bias in control selection.

Discussion

In examining children with DS, a diagnosis of DM occurred 9 times more often in children who developed leukemia and occurred either concurrent with or after the leukemia diagnosis. These results are concordant with those from general population studies of pediatric ALL(14, 16, 24) and suggest that the development of or therapy for ALL induces the DM. That only 14/97 ALL patients acquired DM implicates additional genetic and/or environmental susceptibility factors. Notably, the Childhood Cancer Survivor Study reported increased risks for DM among ALL survivors receiving cranial irradiation and for AML survivors regardless of irradiation therapy,(16) while Hemminki *et al* argued for a common (yet to be identified) viral etiology.(13) Consistent with the results of Pui et al,(14) we observed a greater mean age at leukemia diagnosis in cases that developed diabetes (11.7+/-5.2 years) versus those that did not (3.9+/-3.2 years). Treatment and BMI data were not available for the current analysis.

Contrary to results from a similar study of children with DS(20) and with the inverse(17) and positive associations(18, 19) in studies examining allergic conditions and childhood ALL, we found no consistent associations for asthma, eczema, or other allergies.

The unique design of this study confers notable strengths. Given that COG institutions treat a large majority of pediatric leukemia cases,(25) the use of the COG registry to identify cases resulted in a nearly population-based study. Recruitment of healthy control children with DS from the cases' primary care clinics assured that controls served as reasonable proxies for cases had they not developed leukemia.

Rates of diabetes and hypothyroid disorders reported among our DS controls (2%, 19%, respectively) fall within the ranges reported by others (1-10%, 12-20%).(26, 27) The proportion of controls with asthma diagnoses (15%) was greater than prior reports (3%), suggesting the occurrence of recurrent wheeze due to non-atopic causes.(9) Given the severity of DM, thyroid conditions, and asthma, mothers would be expected to have high

recall of these conditions, while maternal report of eczema would be predicted to be lower.(28, 29) Mothers of children with DS may have even higher recall than those in validation studies, since DS is associated with a complement of co-morbidities.(30) Notably, any misclassification of immune disorders would be expected to be non-differential, as case and control mothers would be similarly motivated in their recall.

An important limitation is the number of subjects that, when coupled with the rarity of the exposures, supplied limited statistical power to detect modest associations. In addition, the interview instrument did not collect exact date/age of DM diagnosis, or presentation, type or duration of DM, although treatment-induced, insulin-dependent, and noninsulin-dependent forms are all plausible.(14, 16, 31) Finally, given that children with DS have been shown to have different immune profiles from children without DS,(4-9) the findings from this study may not be generalizable to children without DS.

These null results indicate asthma, eczema, and hypothyroidism do not confer additional leukemia risk in children with DS, despite the unique cadre of immune-mediating conditions in this population. The DM association implicates the leukemia development or treatment in the etiology of DM and may reflect an underlying genetic susceptibility and/or environmental exposure.

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Table 1

Selected characteristics of 158 acute leukemia cases and 173 controls.

	Controls	Combined Cases			ALL			AML		
	N (%)	N (%)	OR	95% CI	N (%)	OR	95% CI	N (%)	OR	95% CI
Reference age [a]										
<2 years	77 (45%)	63 (40%)			13 (13%)			50 (82%)		
2-5 years	51 (29%)	66 (42%)			55 (57%)			11 (18%)		
≥6 years	45 (26%)	29 (18%)			29 (30%)			0 (0%)		
Gender										
Male	90 (52%)	85 (54%)	1.00		57 (59%)	1.00		28 (46%)	1.00	
Female	83 (48%)	73 (46%)	0.93	(0.60 – 1.43)	40 (41%)	0.76	(0.46 – 1.26)	33 (54%)	1.28	(0.71 – 2.29)
Birth Weight										
≤3500g	136 (79%)	124 (79%)	1.05	(0.62 – 1.79)	80 (82%)	1.28	(0.68 – 2.42)	44 (75%)	0.80	(0.40 – 1.59)
>3500g	37 (21%)	32 (21%)	1.00		17 (18%)	1.00		15 (25%)	1.00	
Number of older siblings										
0	55 (32%)	47 (30%)	1.00		30 (31%)	1.00		17 (28%)	1.00	
1	57 (33%)	56 (35%)	1.15	(0.67 – 1.96)	29 (30%)	0.93	(0.50 – 1.75)	27 (44%)	1.53	(0.75 – 3.12)
2	26 (15%)	30 (19%)	1.35	(0.70 – 2.60)	22 (23%)	1.55	(0.75 – 3.19)	8 (13%)	0.99	(0.38 – 2.60)
3 or more	34 (20%)	25 (16%)	0.86	(0.45 – 1.64)	16 (16%)	0.86	(0.41 – 1.81)	9 (15%)	0.86	(0.34 – 2.14)
Breastfed										
Breast fed only	34 (20%)	25 (16%)	0.77	(0.40 – 1.49)	12 (12%)	0.56	(0.25 – 1.25)	13 (21%)	1.17	(0.49 – 2.78)
Formula only	46 (27%)	44 (28%)	1.00		29 (30%)	1.00		15 (25%)	1.00	
Both	93 (54%)	89 (56%)	1.00	(0.60 – 1.66)	56 (58%)	0.95	(0.54 – 1.69)	33 (54%)	1.09	(0.54 – 2.20)
Maternal age at index child's birth										
<35 years	120 (70%)	95 (60%)	1.00		63 (65%)	1.00		32 (52%)	1.00	
≥35 years	52 (30%)	63 (40%)	1.53	(0.97 – 2.41)	34 (35%)	1.25	(0.73 – 2.11)	29 (48%)	2.09	(1.15 – 3.81)
Maternal ethnicity										
White	152 (88%)	126 (80%)	1.00		79 (81%)	1.00		47 (77%)	1.00	
Non-white	20 (12%)	32 (20%)	1.93	(1.05 – 3.54)	18 (19%)	1.73	(0.87 – 3.46)	14 (23%)	2.26	(1.06 – 4.83)

	Controls	Combined Cases			ALL			AML		
	N (%)	N (%)	OR	95% CI	N (%)	OR	95% CI	N (%)	OR	95% CI
Maternal education										
≤High school graduate	41 (24%)	62 (39%)	1.00		40 (41%)	1.00		22 (36%)	1.00	
Some post-high school	57 (33%)	45 (28%)	0.52	(0.30 – 0.91)	27 (28%)	0.49	(0.26 – 0.91)	18 (30%)	0.59	(0.28 – 1.23)
College graduate	74 (43%)	51 (32%)	0.46	(0.27 – 0.78)	30 (31%)	0.42	(0.23 – 0.76)	21 (34%)	0.53	(0.26 – 1.08)
Maternal smoking during pregnancy										
Yes	24 (14%)	27 (17%)	1.28	(0.70 – 2.33)	16 (16%)	1.23	(0.62 – 2.44)	11 (18%)	1.37	(0.62 – 2.99)
No	149 (86%)	131 (83%)	1.00		81 (84%)	1.00		50 (82%)	1.00	
Marital status										
Married/living as married	152 (89%)	140 (89%)	1.00		89 (92%)	1.00		51 (84%)	1.00	
Separated/divorced/widowed	14 (8%)	12 (8%)	0.93	(0.42 – 2.08)	7 (7%)	0.85	(0.33 – 2.19)	5 (8%)	1.06	(0.36 – 3.10)
Never married	4 (2%)	6 (4%)	1.63	(0.45 – 5.89)	1 (1%)	0.43	(0.05 – 3.88)	5 (8%)	3.72	(0.96 – 14.41)
Household income										
≤$30,000	57 (33%)	57 (37%)	1.00		37 (39%)	1.00		20 (33%)	1.00	
$30,001 - $50,000	41 (24%)	43 (28%)	1.05	(0.60 – 1.84)	22 (23%)	0.83	(0.43 – 1.60)	21 (35%)	1.46	(0.70 – 3.04)
>$50,000	74 (43%)	56 (36%)	0.76	(0.46 – 1.25)	37 (39%)	0.77	(0.44 – 1.36)	19 (32%)	0.73	(0.36 – 1.50)

Abbreviations: OR: odds ratio; 95% CI: 95% confidence interval; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia

[a]Reference age, the frequency matching factor, was not evaluated with respect to odds of leukemia.

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Table 2

Associations between allergic and autoimmune diseases, respectively, and acute leukemia in children with Down syndrome.

	Controls	Combined Cases			ALL			AML		
	N (%)	N (%)	OR [a]	95% CI	N (%)	OR [a]	95% CI	N (%)	OR [a]	95% CI
Asthma (any)										
Yes	26 (15%)	21 (13%)	0.86	(0.45 – 1.66)	16 (16%)	1.16	(0.56 – 2.40)	5 (8%)	0.56	(0.18 – 1.75)
No	147 (85%)	136 (87%)	1.00		81 (84%)	1.00		55 (92%)	1.00	
Asthma ≥ 6 months prior to leukemia										
Yes	17 (10%)	10 (6%)	0.62	(0.27 – 1.47)	9 (9%)	0.88	(0.36 – 2.17)	1 (2%)	0.28	(0.03 – 2.56)
No	156 (90%)	147 (94%)	1.00		88 (91%)	1.00		59 (98%)	1.00	
Eczema (any)										
Yes	29 (17%)	21 (13%)	0.88	(0.46 – 1.68)	15 (15%)	1.03	(0.49 – 2.13)	6 (10%)	0.74	(0.26 – 2.13)
No	143 (83%)	135 (87%)	1.00		82 (85%)	1.00		53 (90%)	1.00	
Eczema ≥ 6 months prior to leukemia										
Yes	18 (10%)	12 (8%)	0.82	(0.36 – 1.86)	11 (11%)	1.10	(0.46 – 2.62)	1 (2%)	0.46	(0.05 – 4.15)
No	154 (90%)	144 (92%)	1.00		86 (89%)	1.00		58 (98%)	1.00	
Asthma and/or Eczema (any)										
Yes	46 (27%)	41 (26%)	1.07	(0.63 – 1.80)	30 (31%)	1.47	(0.81 – 2.68)	11 (19%)	0.71	(0.31 – 1.65)
No	126 (73%)	115 (74%)	1.00		67 (69%)	1.00		48 (81%)	1.00	
Allergies ≥ 6 months prior to leukemia (includes inhaled, medication, food, and contact allergies) [b]										
Yes	20 (18%)	17 (12%)	0.82	(0.39 – 1.73)	14 (15%)	0.84	(0.38 – 1.85)	3 (7%)	3.89	(0.50 – 29.95)
No	94 (82%)	119 (87%)	1.00		81 (85%)	1.00		38 (93%)	1.00	
Any allergic condition ≥ 6 months prior to leukemia (includes asthma, eczema, and allergies)[c]										
Yes	39 (23%)	34 (22%)	1.05	(0.60 – 1.84)	29 (30%)	1.40	(0.76 – 2.59)	5 (8%)	0.93	(0.29 – 2.96)
No	130 (77%)	122 (78%)	1.00		68 (70%)	1.00		54 (92%)	1.00	
Diabetes (any)										
Yes	3 (2%)	15 (9%)	9.23	(2.33 – 36.59)	14 (14%)	7.51	(1.91 – 29.50)	1 (2%)	4.77	(0.23 – 97.34)
No	170 (98%)	143 (91%)	1.00		83 (86%)	1.00		60 (98%)	1.00	

	Controls	Combined Cases			ALL			AML		
	N (%)	N (%)	OR [a]	95% CI	N (%)	OR [a]	95% CI	N (%)	OR [a]	95% CI
Diabetes ≥ 6 months prior to leukemia										
Yes	1 (1%)	1 (1%)	0.92	(0.05 – 15.41)	0 (0%)	--		1 (2%)	187.6	(0.46 - >999)
No	172 (99%)	157 (99%)	1.00		97 (100%)	1.00		60 (98%)	1.00	
Hypothyroid conditions (any)										
Yes	33 (19%)	19 (12%)	0.66	(0.35 – 1.24)	13 (13%)	0.73	(0.35 – 1.53)	6 (10%)	0.70	(0.25 – 1.98)
No	140 (81%)	138 (88%)	1.00		84 (87%)	1.00		54 (90%)	1.00	
Hypothyroid conditions ≥ 6 months prior to leukemia										
Yes	15 (9%)	9 (6%)	0.72	(0.29 – 1.78)	6 (6%)	0.75	(0.27 – 2.11)	3 (5%)	1.66	(0.36 – 7.69)
No	158 (91%)	148 (94%)	1.00		91 (94%)	1.00		57 (95%)	1.00	

Abbreviations: OR: odds ratio; 95% CI: 95% confidence interval; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia

[a] Adjusted for child's reference age (continuous), number of older siblings (0 vs. 1 vs. 2 vs. 3 or more), maternal race (white vs. non-white),maternal education (≤HS vs. some post-HS vs. college grad) and maternal age (<35 vs. ≥35 years).

[b] Mothers were only asked about prior diagnosis of allergies ≥ 6 months prior to leukemia in those diagnosed at ≥2.5 years of age.

[c] For this analysis, subjects not asked about allergy history ≥ 6 months prior to leukemia were classified as not having an allergy.

Table 3

Associationsbetween allergic and autoimmune diseases, respectively, among siblings and acute leukemia in children with Down syndrome.[a, b]

	Controls	Combined Cases			ALL			AML		
	N (%)	N (%)	OR [c]	95% CI	N (%)	OR [c]	95% CI	N (%)	OR [c]	95% CI
Asthma (any)										
Yes	25 (16%)	25 (19%)	1.20	(0.61 – 2.36)	15 (18%)	0.96	(0.44 – 2.08)	10 (20%)	1.81	(0.65 – 5.10)
No	127 (84%)	109 (81%)	1.00		70 (82%)	1.00		39 (80%)	1.00	
Eczema (any)										
Yes	34 (22%)	19 (14%)	0.53	(0.27 – 1.04)	10 (12%)	0.51	(0.22 – 1.16)	9 (19%)	0.62	(0.24 – 1.57)
No	118 (78%)	114 (86%)	1.00		75 (88%)	1.00		39 (81%)	1.00	
Asthma and/or Eczema (any)										
Yes	47 (31%)	34 (26%)	0.77	(0.44 – 1.36)	20 (24%)	0.68	(0.35 – 1.33)	14 (29%)	0.90	(0.39 – 2.08)
No	105 (69%)	99 (74%)	1.00		65 (76%)	1.00		34 (71%)	1.00	
Diabetes (any)										
Yes	1 (1%)	0 (0%)	--		0 (0%)	--		0 (0%)	--	
No	151 (99%)	135 (100%)			85 (100%)			50 (100%)		
Hypothyroid conditions (any)										
Yes	2 (1%)	1 (1%)	0.50	(0.04 – 5.91)	1 (1%)	0.59	(0.05 – 7.10)	0 (0%)	--	
No	150 (99%)	133 (99%)	1.00		84 (99%)	1.00		49 (100%)		

Abbreviations: OR: odds ratio; 95% CI: 95% confidence interval; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia

[a] Includes only index children with at least one sibling (n_{cases}=135; $n_{controls}$=152).

[b] Mothers were not asked about other allergies in siblings.

[c] Adjusted for child's reference age (continuous), number of siblings (1 vs. 2 vs. 3 or more), maternal race (white vs. non-white),maternal education (≤HS vs. some post-HS vs. college grad) and maternal age (<35 vs. ≥35 years).