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 have unique immune profiles and increased leukemia susceptibility.

Methods: Mothers of 158 children with Down syndrome diagnosed with acute leukemia at 0 to 19 years in 1997 to 2002 and 173 children with Down syndrome 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 (OR = 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 Down syndrome who develop leukemia have increased diabetes risk, likely due to treatment and underlying susceptibility factors. Cancer Epidemiol Biomarkers Prev; 24(2): 454–8. ©2014 AACR.

Introduction

Children with Down syndrome 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 Down syndrome 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 natural killer cells, and increased numbers of proinflammatory CD14++CD16+ monocytes (4). Differences in cytokine levels have also been observed (5). For example, expression of IFNγ, 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 Down syndrome (6, 7). These differences correspond to an altered distribution of comorbidities, in which children with Down syndrome have increased rates of infections and autoimmunity (e.g., diabetes mellitus, 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 diabetes mellitus and acute lymphoblastic leukemia (ALL); however, diabetes mellitus often presents after the leukemia diagnosis and may be self-limiting (12, 13). Notably, the development of transient diabetes mellitus in approximately 10% of patients with ALL 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 diabetes mellitus is managed by monitoring glucose levels, administration of IV fluids, dietary modifications, increased exercise, and administration of insulin as needed (15). Children with Down syndrome are one of the groups at higher risk of transient diabetes mellitus (14). In a series of 421 childhood ALL patients, host factors associated with treatment-related hyperglycemia included Down syndrome [response rate (RR) = 7.17], age ≥10 years (RR = 6.68), and obesity (RR = 8.53; ref. 14). The diabetes mellitus often resolves after the discontinuation of the responsible therapeutic agent(s) (refs. 14, 15); however, ALL survivors are at increased risk for chronic diabetes mellitus following treatment (16). To our knowledge, no prior studies have examined autoimmune diseases as risk factors for acute leukemia in children with Down syndrome.

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 Down syndrome reported an increased odds of acute leukemia associated with asthma [OR = 4.18; 95% confidence interval (CI) 1.47–11.87], and an inverse association with skin allergies (OR = 0.42; 95% CI 0.20–0.91; ref. 20).
Here, we tested the null hypothesis of no association between asthma, eczema, allergies, diabetes mellitus, or hypothyroidism in children with Down syndrome 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 Down syndrome diagnosis, an acute leukemia diagnosis between 0 and 19 years of age in Jan 1, 1997 to Oct 31, 2002 at a U.S. or Canadian COG institution, a residential telephone line, and a consenting biologic 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 Down syndrome generated by the cases’ providers. Like cases, control children with a prior diagnosis of Down syndrome (but no cancer diagnosis), residential telephone line, and consenting biologic mother that spoke English were eligible. Controls were frequency matched to cases in the age groupings: 0, 1 to 3, 4 to 6, 7 to 10, 11 to 14, and 15 to 18 years. Down syndrome 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 before 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 before the leukemia diagnosis.

Data on prior diagnosis of asthma, eczema, allergies, diabetes mellitus, thyroid conditions, and covariates were ascertained by Institutional Review Boards of the University of Minnesota and participating COG institutions and participating COG institutions approved the study.

Table 1. Selected characteristics of 158 acute leukemia cases and 173 controls

<table>
<thead>
<tr>
<th>Reference agea</th>
<th>Controls N (%)</th>
<th>Combined cases N (%)</th>
<th>ALL N (%)</th>
<th>AML N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 years</td>
<td>77 (45%)</td>
<td>13 (13%)</td>
<td>50 (82%)</td>
<td></td>
</tr>
<tr>
<td>2–5 years</td>
<td>51 (29%)</td>
<td>55 (57%)</td>
<td>11 (18%)</td>
<td></td>
</tr>
<tr>
<td>&gt;6 years</td>
<td>45 (26%)</td>
<td>29 (30%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>90 (52%)</td>
<td>57 (59%)</td>
<td>28 (46%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>83 (48%)</td>
<td>40 (41%)</td>
<td>33 (54%)</td>
<td>1.28 (0.71–2.29)</td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3,500 g</td>
<td>136 (79%)</td>
<td>80 (82%)</td>
<td>44 (75%)</td>
<td>0.80 (0.40–1.59)</td>
</tr>
<tr>
<td>&gt;3,500 g</td>
<td>37 (21%)</td>
<td>17 (18%)</td>
<td>15 (25%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Number of older siblings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>55 (32%)</td>
<td>30 (31%)</td>
<td>17 (28%)</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>57 (33%)</td>
<td>29 (30%)</td>
<td>27 (44%)</td>
<td>1.53 (0.75–3.12)</td>
</tr>
<tr>
<td>2</td>
<td>26 (15%)</td>
<td>22 (23%)</td>
<td>8 (13%)</td>
<td>0.99 (0.38–2.60)</td>
</tr>
<tr>
<td>3 or more</td>
<td>34 (20%)</td>
<td>16 (18%)</td>
<td>9 (15%)</td>
<td>0.86 (0.34–2.14)</td>
</tr>
<tr>
<td>Breast fed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast fed only</td>
<td>34 (20%)</td>
<td>12 (12%)</td>
<td>13 (21%)</td>
<td>1.17 (0.49–2.78)</td>
</tr>
<tr>
<td>Formula only</td>
<td>46 (27%)</td>
<td>29 (30%)</td>
<td>15 (25%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Both</td>
<td>93 (54%)</td>
<td>56 (58%)</td>
<td>35 (54%)</td>
<td>1.09 (0.54–2.20)</td>
</tr>
<tr>
<td>Maternal age at index child’s birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35 years</td>
<td>120 (70%)</td>
<td>63 (65%)</td>
<td>32 (52%)</td>
<td>1.00</td>
</tr>
<tr>
<td>≥35 years</td>
<td>52 (30%)</td>
<td>34 (35%)</td>
<td>29 (48%)</td>
<td>2.09 (1.15–3.81)</td>
</tr>
<tr>
<td>Maternal ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>152 (88%)</td>
<td>79 (81%)</td>
<td>47 (77%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-white</td>
<td>20 (12%)</td>
<td>18 (19%)</td>
<td>14 (23%)</td>
<td>2.26 (1.06–4.83)</td>
</tr>
<tr>
<td>Maternal education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤High school graduate</td>
<td>41 (24%)</td>
<td>40 (41%)</td>
<td>22 (36%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Some post-high school</td>
<td>57 (33%)</td>
<td>27 (28%)</td>
<td>18 (30%)</td>
<td>0.59 (0.28–123)</td>
</tr>
<tr>
<td>College graduate</td>
<td>74 (43%)</td>
<td>50 (31%)</td>
<td>21 (34%)</td>
<td>0.53 (0.26–108)</td>
</tr>
<tr>
<td>Maternal smoking during pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24 (14%)</td>
<td>16 (16%)</td>
<td>11 (18%)</td>
<td>1.37 (0.62–2.99)</td>
</tr>
<tr>
<td>No</td>
<td>149 (86%)</td>
<td>81 (84%)</td>
<td>50 (82%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/living as married</td>
<td>152 (89%)</td>
<td>89 (92%)</td>
<td>51 (84%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Separated/divorced/widowed</td>
<td>14 (8%)</td>
<td>7 (7%)</td>
<td>5 (8%)</td>
<td>1.06 (0.36–3.10)</td>
</tr>
<tr>
<td>Never married</td>
<td>4 (2%)</td>
<td>1 (1%)</td>
<td>3 (5%)</td>
<td>3.72 (0.96–14.41)</td>
</tr>
<tr>
<td>Household income</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤$30,000</td>
<td>57 (33%)</td>
<td>57 (39%)</td>
<td>20 (33%)</td>
<td>1.00</td>
</tr>
<tr>
<td>$30,001–$50,000</td>
<td>41 (24%)</td>
<td>22 (23%)</td>
<td>14 (23%)</td>
<td>1.46 (0.70–3.04)</td>
</tr>
<tr>
<td>&gt;$50,000</td>
<td>74 (43%)</td>
<td>57 (39%)</td>
<td>19 (32%)</td>
<td>0.73 (0.36–1.50)</td>
</tr>
</tbody>
</table>

*aReference 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

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Combined cases</th>
<th>ALL</th>
<th>AML</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Asthma (any)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26 (15%)</td>
<td>21 (13%)</td>
<td>16 (16%)</td>
<td>0.86 (0.45–1.66)</td>
</tr>
<tr>
<td>No</td>
<td>143 (85%)</td>
<td>156 (87%)</td>
<td>81 (84%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Asthma ≥ 6 months before leukemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17 (10%)</td>
<td>10 (6%)</td>
<td>9 (9%)</td>
<td>0.62 (0.27–1.47)</td>
</tr>
<tr>
<td>No</td>
<td>156 (90%)</td>
<td>147 (94%)</td>
<td>88 (99%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Eczema (any)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29 (17%)</td>
<td>21 (13%)</td>
<td>15 (15%)</td>
<td>1.03 (0.49–2.13)</td>
</tr>
<tr>
<td>No</td>
<td>143 (83%)</td>
<td>135 (87%)</td>
<td>82 (85%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Eczema ≥ 6 months before leukemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18 (10%)</td>
<td>12 (8%)</td>
<td>11 (17%)</td>
<td>1.10 (0.46–2.62)</td>
</tr>
<tr>
<td>No</td>
<td>154 (90%)</td>
<td>144 (92%)</td>
<td>86 (89%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Asthma and/or eczema (any)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>46 (27%)</td>
<td>41 (26%)</td>
<td>30 (31%)</td>
<td>1.47 (0.81–2.68)</td>
</tr>
<tr>
<td>No</td>
<td>126 (73%)</td>
<td>115 (74%)</td>
<td>67 (69%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Allergies ≥ 6 months before leukemia (includes inhaled, medication, food, and contact allergies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20 (18%)</td>
<td>17 (12%)</td>
<td>14 (15%)</td>
<td>0.84 (0.38–1.85)</td>
</tr>
<tr>
<td>No</td>
<td>94 (82%)</td>
<td>119 (87%)</td>
<td>81 (85%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Any allergic condition ≥ 6 months before leukemia (includes asthma, eczema, and allergies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39 (23%)</td>
<td>34 (22%)</td>
<td>29 (30%)</td>
<td>1.40 (0.76–2.59)</td>
</tr>
<tr>
<td>No</td>
<td>130 (77%)</td>
<td>122 (78%)</td>
<td>68 (70%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes (any)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (2%)</td>
<td>15 (9%)</td>
<td>14 (14%)</td>
<td>7.51 (1.91–29.50)</td>
</tr>
<tr>
<td>No</td>
<td>170 (98%)</td>
<td>143 (91%)</td>
<td>83 (86%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes ≥ 6 months before leukemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>—</td>
</tr>
<tr>
<td>No</td>
<td>172 (99%)</td>
<td>157 (99%)</td>
<td>97 (100%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypothyroid conditions (any)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (19%)</td>
<td>19 (12%)</td>
<td>13 (13%)</td>
<td>0.73 (0.35–1.53)</td>
</tr>
<tr>
<td>No</td>
<td>140 (81%)</td>
<td>138 (88%)</td>
<td>84 (87%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypothyroid conditions ≥ 6 months before leukemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (9%)</td>
<td>9 (6%)</td>
<td>6 (6%)</td>
<td>0.75 (0.27–2.11)</td>
</tr>
<tr>
<td>No</td>
<td>154 (91%)</td>
<td>148 (94%)</td>
<td>91 (94%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*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 graduate), and maternal age (<35 vs. ≥35 years).

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

For this analysis, subjects not asked about allergy history ≥ 6 months before leukemia were classified as not having an allergy.

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.). ORs and 95% confidence intervals were generated for two time periods, any time and 6 months or more before 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 and 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 diabetes mellitus 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 and 3 controls). Because 14 of 15 cases (all of them with ALL) and 2 of 3 controls were diagnosed with diabetes mellitus ≤6 months preceding or after the leukemia diagnosis, the association was no longer observed in examining only diabetes mellitus diagnosed ≥6 months before 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 Down syndrome, a diagnosis of diabetes mellitus occurred nine times more often in children who developed leukemia and occurred either concurrently 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 diabetes mellitus. That only 14 of 97 ALL patients acquired diabetes mellitus implicates additional genetic and/or environmental susceptibility factors. Notably, the Childhood Cancer Survivor Study reported increased risks for diabetes mellitus...
Among ALL survivors receiving cranial irradiation and for AML survivors, regardless of irradiation therapy (16), whereas Hemminki and colleagues (13) argued for a common (yet to be identified) viral etiology. Consistent with the results of Pui and colleagues (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 body mass index data were not available for this analysis.

Contrary to results from a similar study of children with Down syndrome (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 Down syndrome 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 Down syndrome controls (2%, 19%) were within the ranges reported by others (1%–10%, 12%–20%; refs. 26, 27). The proportion of controls with asthma diagnoses (15%) was greater than prior reports (3%), suggesting the occurrence of recurrent wheeze due to nonatopic causes (9). Given the severity of diabetes mellitus, thyroid conditions, and asthma, mothers would be expected to have high recall of these conditions, whereas maternal report of eczema would be predicted to be lower (28, 29). Mothers of children with Down syndrome may have even higher recall than those in validation studies, because Down syndrome is associated with a complement of comorbidities (30). Notably, any misclassification of immune disorders would be expected to be nondifferential, 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 diabetes mellitus diagnosis, or presentation, type or duration of diabetes mellitus, although treatment-induced, insulin-dependent, and noninsulin-dependent forms are all plausible (14, 16, 31). Finally, given that children with Down syndrome have been shown to have different immune profiles from children without Down syndrome (4–9), the findings from this study may not be generalizable to children without Down syndrome.

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

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: A.M. Linabery, A.S. Gamis, J.A. Ross
Development of methodology: M.A. Roesler, L.G. Spector, J.A. Ross
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.A. Ross, L.G. Spector, A.S. Gamis, N.A. Heerema, J.A. Ross
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.M. Linabery, W. Li, M.A. Roesler, L.G. Spector, J.A. Ross
Writing, review, and/or revision of the manuscript: A.M. Linabery, W. Li, M.A. Roesler, L.G. Spector, A.S. Gamis, A.F. Olshan, N.A. Heerema, J.A. Ross
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.A. Roesler, L.G. Spector, J.A. Ross
Study supervision: J.A. Ross

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