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Evaluation of maternal health and labor and delivery conditions as risk factors for childhood leukemias in children with Down syndrome

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ABSTRACT

Children with Down syndrome (DS) have a remarkably high risk of developing leukemia during childhood; the mechanisms driving that risk are not well understood, and no clear prevention strategies exist. We conducted a nested case-control study in a Texas DS birth cohort to investigate possible links between maternal health, labor/delivery conditions, and leukemia risk. For most of the factors studied there was no evidence of an increased risk of total leukemias, or the subtypes acute lymphoid or acute myeloid leukemia. Ultrasound use showed an almost 2-fold increased odds of leukemia, but this result is likely an example of confounding by indication. There was a pattern of increased risk seen for presence of co-occurring heart anomalies, including tetralogy of Fallot, ventricular septal defects, atrial septal defects, and patent ductus arteriosus. Further investigation of the links between co-occurring heart defects in children with DS and development of leukemia may provide new understanding of cancer mechanisms, and ultimately lead to prevention opportunities for this high-risk population.

1. Introduction

Children with trisomy 21, or Down syndrome (DS), face a variety of health challenges, including a remarkably high risk for developing leukemia in their childhood years. Previous research indicates that children with DS are more than 50 times as likely to develop leukemia before age 5 years than non-DS children; this risk decreases dramatically with age, pointing to a likely intrauterine origin [1]. Although epidemiological studies of leukemia risk among children with DS have investigated a variety of environmental exposures [2–4], maternal health conditions during pregnancy [5,6] and health conditions of children with DS in early childhood [7,8], no clear pattern of risk has been identified. As the birth prevalence of DS is increasing around the world [9], it is also likely mirrored by an increasing prevalence of leukemia in this high-risk population.

A recent review noted that essentially only two research teams have produced all the epidemiological information available about potential risk factors for leukemia among children with DS [10]; clearly additional epidemiological studies in this population are needed. Mezei et al. [10] noted in their review that there is currently no evidence to suggest that potentially carcinogenic environmental exposures act differently in DS versus non-DS children, leading them to conclude that studying risk factors for leukemia among children with DS may also contribute to the understanding of childhood leukemia in the general population. To this end, we used a nested case-control study design to evaluate whether factors related to maternal health and the circumstances of labor and delivery, including the presence of co-occurring birth defects, influenced risk of subsequent development of leukemia in children born with DS in the state of Texas.

2. Materials and methods

2.1. Study subjects

Birth certificate data files for the birth cohort consisting of children born to Texas residents between January 1, 1996 and December 31, 2009 were provided by the Vital Statistics Unit and the Center for Health Statistics of the Texas Department of State

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Health Services. Children with birth defects were identified through the Texas Birth Defects Registry (TBDR). The TBDR is an active surveillance system which includes all cases of structural or chromosomal birth defects among children born in Texas that are diagnosed by a physician and recorded in medical records. Diagnoses of birth defects are accepted by TBDR if made prenatally or up to the first birthday of the child. Texas children diagnosed with cancer before age 15 years were identified by the Texas Cancer Registry (TCR), a statewide population-based registry that collects data on incident cases of cancer occurring among Texas residents. Link Plus, a software linkage tool developed at CDC's Division of Cancer Prevention and Control, was used to link TCR records with birth records and with TBDR data files, resulting in a data file of all Texas births for the study period with information on any birth defects and/or cancers subsequently diagnosed among these births. Details of the matching protocol have been previously published [11].

For this study, all DS births were identified within the full birth cohort and this DS-only birth cohort served as the source for all study subjects for the nested case-control analysis. Allleukemia cases among children with DS were included in the study population (n = 93). DS controls were randomly selected at a 4:1 ratio of cases to controls (n = 372 DS children without a cancer diagnosis), using frequency matching within 30 days of birth date.

2.2. Statistical analyses

Data items were provided by the cancer and birth defects registries and the Vital Statistics Unit of the Texas Department of State Health Services for cancer diagnosis, recorded birth defects, and data recorded on birth certificates; no additional data were collected. A new birth certificate version was introduced in Texas in 2005, so not all variables were available for all study years; variable names were harmonized where possible. While the list of possible data items for pregnancy history and obstetric procedures was extensive, for many of the items there were no exposed cases in our study population (e.g. chronic hypertension, eclampsia, forceps delivery) and so these variables were not evaluated. Risk associated with any heart defect was evaluated; specific types of heart defects were evaluated where numbers were sufficient.

We evaluated risk of all leukemias, as well as acute lymphoid leukemia (ALL) and acute myeloid leukemia (AML). Unadjusted odds ratios (ORs) and 2-sided 95% confidence intervals (CIs) were calculated using unconditional logistic regression. In this study, statistical significance refers to CIs for ORs that exclude 1. Additional reported BDs for study subjects were treated as continuous variables in the analysis; this assumes that the effect of each additional birth defect is linear on the log-odds scale. Analyses were performed using R Statistical Software (version 3.1.1; R Foundation for Statistical Computing, Vienna, Austria).

Human subjects research approval for this study was granted by the Institutional Review Boards of the Texas Department of State Health Services and Oregon State University.

3. Results

More than 85% of the study mothers were under age 40 years at the time of the DS birth, however, a slightly higher proportion of case mothers than control mothers were over age 40 years (Table 1). Approximately half of the mothers were Hispanic; case and control mothers had similar race/ethnicity distributions. Fewer case mothers and fathers had less than a high school education compared to controls; a greater proportion of case than control mothers had educational attainment beyond high school. The proportion of mothers who had pregnancy length less than 35 weeks and the proportion with babies weighing less than 1500 g was higher in controls than cases. Approximately 70% of study children had at least one additional recorded birth defect, with more cases (17.2%) than controls (11.8%) having three or more additional anomalies. Heart defects were the most common type of co-occurring birth defect, with 69.9% of controls and 77.4% of cases having at least one type of heart defect.

Table 1
Characteristics of Down syndrome cases and controls, Texas 1996–2009.

Characteristic		Controls	Cases	Total
Mother's Age	<40years	321 (86.3%)	77 (82.8%)	398 (85.6%)
	40+ years	51 (13.7%)	16 (17.2%)	67 (14.4%)
Mother's Race	White	149 (40.1%)	34 (36.6%)	183 (39.4%)
	Black	24 (6.5%)	8 (8.6%)	32 (6.9%)
	Hispanic	192 (51.6%)	49 (52.7%)	241 (51.8%)
	Other	7 (1.9%)	2 (2.2%)	9 (1.9%)
Mother's Education	<High School	55 (15.2%)	11 (12.1%)	66 (14.5%)
	High School	163 (44.9%)	39 (42.9%)	202 (44.5%)
	>High School	145 (39.9%)	41 (45.1%)	186 (41.0%)
Child Sex	Male	190 (51.1%)	50 (53.8%)	240 (51.6%)
	Female	182 (48.9%)	43 (46.2%)	225 (48.4%)
Pregnancy Length	<35 weeks	48 (13.7%)	4 (4.7%)	52 (11.9%)
	35–36 weeks	49 (14.0%)	15 (17.6%)	64 (14.7%)
	37+ weeks	254 (72.4%)	66 (77.6%)	320 (73.4%)
Birth Weight	<1500 g	16 (4.3%)	2 (2.2%)	18 (3.9%)
	1500–2500 grams	68 (18.5%)	16 (17.2%)	84 (18.2%)
	2500–4000 grams	272 (73.9%)	71 (76.3%)	343 (74.4%)
	>4000 g	12 (3.3%)	4 (4.3%)	16 (3.5%)
Father's Age	<40years	254 (79.6%)	64 (75.3%)	318 (78.7%)
	40+ years	65 (20.4%)	21 (24.7%)	86 (21.3%)
Father's Education	<High School	43 (13.7%)	8 (10.0%)	51 (12.9%)
	High School	135 (42.9%)	37 (46.3%)	172 (43.5%)
	>High School	137 (43.5%)	35 (43.8%)	172 (43.5%)
Additional birth defects	0	113 (30.4%)	22 (23.7%)	135 (29.0%)
	1	108 (29.0%)	32 (34.4%)	140 (30.1%)
	2	107 (28.8%)	23 (24.7%)	130 (28.0%)
	3	41 (11.0%)	15 (16.1%)	56 (12.0%)
	4	3 (0.8%)	1 (1.1%)	4 (0.9%)
	Heart defect	260 (69.9%)	72 (77.4%)	332 (71.4%)