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Original article

The role of parental and perinatal characteristics on Langerhans cell histiocytosis: characterizing increased risk among Hispanics

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ABSTRACT

Purpose: Potential roles of inherited and environmental risk factors in pathogenesis of Langerhans cell histiocytosis (LCH), a myeloid neoplastic disorder, are undefined. We therefore evaluated the role of parental and perinatal factors on the risk of this childhood cancer.
Methods: Information on LCH cases ($n = 162$) for the period 1995–2011 was obtained from the Texas Cancer Registry. Birth certificate controls were frequency-matched on year of birth at a ratio of 10:1 for the same period. Variables evaluated included parental age, race/ethnicity, size for gestational age, and birth order. Logistic regression was used to generate an adjusted odds ratio (aOR) and 95% confidence interval (CI) testing the association between each factor and LCH.
Results: Few perinatal or parental factors were associated with LCH risk, with the exception of race/ethnicity. Mothers of Hispanic ethnicity were more likely to have children who developed LCH compared to non-Hispanic whites (aOR: 1.51; 95% CI: 1.02–2.25). This risk increased when both parents were Hispanic (aOR: 1.80; 95% CI: 1.13–2.87). Non-Hispanic black mothers were suggested as less likely to give birth to offspring who developed LCH compared to non-Hispanic whites (aOR: 0.50; 95% CI: 0.24–1.02).
Conclusions: LCH is characterized by somatic mutations in *MAPK* pathway genes in myeloid precursors. Increased risk for LCH in children of Hispanic parents suggests potential impact of inherited factors on LCH pathogenesis.

Introduction

Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasia and the most common of all the histiocytic disorders [1]. While LCH may occur at any age, the median age at diagnosis is 30 months with an estimated incidence of five cases per 1,000,000 children ages 0–14 [2]. Incidence is highest in infants less than 1 year and decreases steadily with increasing age [3]. Despite a relatively high 5-year survival rate of ~85% for patients with hematopoietic organ involvement and ~99% for multisystem patients without risk organ involvement [4,5], up-front chemotherapy fails in over 50% of cases. Higher risk of long-term sequelae associated with treatment failure includes potential for progressive LCH-associated neurodegenerative disease [5,6]. In addition to challenges associated with treatment, children with LCH experience high relapse rates, nearing 50% within the first 2 years and over 40% of those experience a second relapse event [7]. These characteristics underscore the need to identify risk predictors for the prevention of pediatric LCH and improved understanding of mechanisms of pathogenesis.

As with many pediatric cancers, few well-established risk factors for LCH exist. In LCH, mutually exclusive *MAPK* pathway activating somatic mutations have been identified in approximately 85% of cases, and ERK activation is universal in LCH dendritic cells [8,9]. However, random acquisition of cell-specific somatic mutations may not completely explain LCH pathogenesis. As in other pediatric cancers (e.g., B-cell acute lymphoblastic leukemia [ALL]) [10], the incidence of LCH appears to vary by race/ethnicity, which suggests a role for inherited genetic factors in LCH susceptibility [11–13]. In addition, maternal and neonatal infections [13,14] and lack of childhood vaccinations [14] are suspected to increase LCH

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risk. Notably, there have been several studies evaluating the role of maternal and perinatal characteristics on other pediatric hematologic malignancies to determine the impact of inborn variation on disease risk [15–17]. However, there have been few population-based efforts to determine the role of these factors on the risk of LCH. Therefore, we leveraged one of the world's largest population-based cancer registries to evaluate the role of parental and perinatal characteristics on the risk of developing pediatric LCH in a state characterized by a growing and diverse population.

Material and methods

Study design and participant ascertainment

We performed a case-control study to investigate the role of parental and perinatal characteristics on LCH susceptibility. Our case eligibility criteria included being born in Texas between the years 1995–2011 and being diagnosed with LCH during the same time period. The Texas Cancer Registry (TCR) provided information on the cases ($n = 162$) who fulfilled these criteria. Based on this, our case population included children and adolescents up to 16 years of age, which captured the most at-risk age groups in terms of those who present with LCH [2,3]. The TCR is one of the world's largest, statewide population-based cancer registries, and during the study period was "Gold Certified" by the North American Association of Central Cancer Registries [18]. The selection of LCH histologic subtypes in this study was based on the most recent version of ICD-O3 histologic codes (ICD-O3) with malignant behavior and included LCH, not otherwise specified (9751/3) and LCH, disseminated (9754/3). Given a previous debate as to whether LCH was an inflammatory disorder or myeloid neoplasia, LCH cases reported to the Surveillance, Epidemiology, and End Results program (SEER) registry before 2009 would most likely include those with high-risk organ involvement sites (spleen, liver, and bone marrow).

Data on case, parental, and perinatal characteristics were obtained from Texas birth certificates that were probabilistically linked and provided by the Center for Health Statistics, Texas Department of State Health Services. Approximately 87% of LCH cases registered in the TCR for children and adolescents born and diagnosed in the period of 1995–2011 were successfully linked to Texas birth records by the Center for Health Statistics. Eligibility criteria for controls included being born in Texas during 1995–2011 without a history of cancer during that same time period. Parental and perinatal characteristic data for all children born in Texas, who fulfilled these criteria served as the eligibility pool from which controls were selected. As with cases, eligible controls were between the ages of 0–16 years. We randomly selected 10 noncancer controls per case matched on year of birth using a random-number generator ($n = 1620$). The Institutional Review Boards at Baylor College of Medicine and the Texas Department of State Health Services approved this study.

Parental and perinatal variables

Data obtained from birth records for cases and controls included infant sex; date of birth; birth weight in grams; plurality (singleton and ≥2); maternal and paternal age (<20, 20–24, 25–29, 30–35, and ≥35 years); maternal and paternal race/ethnicity (non-Hispanic white [NHW], Hispanic [Hisp], non-Hispanic black [NHB], and non-Hispanic other [NHO]); maternal education (<high school, high school, and >high school); maternal nativity (United States, Mexico, and other foreign country); residence at time of delivery in a county on the United States-Mexico border (vs. not); urban or rural residence at delivery identified by 2000 census tract data; history of other live births (1, 2, and ≥3); maternal smoking history during pregnancy (yes or no); mode of delivery (vaginal spontaneous, vaginal forceps or vacuum, and cesarean); history of infant Hepatitis B vaccination before hospital discharge (yes or no); and term of birth (pre- and early-term defined as <39 weeks, full term defined as 39–41 weeks, and late-term defined as ≥41 weeks). Season of birth was based on birth date and classified as spring, summer, fall, or winter based on solstice and equinox dates. Birth records for cases and controls also provided the date last normal menses began (LMP) and clinical estimate of gestation in weeks. LMP was used to determine the gestational age for most births [19,20]. However, if the LMP date was missing or there was an absolute difference greater than 2 weeks between the LMP date and clinical estimate of gestational age, the clinical estimate was used per established guidelines [19,21]. If both LMP date and clinical estimate of gestational age were missing, that birth was excluded from the gestational age-specific analyses. Births were classified as small-for-gestational-age if the birth weight was <10th percentile for their gestational age or large-for-gestational-age if the birth weight was greater than 90th percentile for their gestational age. These estimates were based on 2009–2010 U.S. live birth data stratified by infant sex [22].

Maternal prepregnancy body mass index was calculated from 2005 to 2011 birth records because maternal height and weight was only collected from 2005 onward. A subgroup analysis tested for an association between maternal body mass index and pediatric LCH. History of the infant being breastfed before hospital discharge was also only available in birth records from 2005 onward (yes or no). To generate a combined parental race/ethnicity variable representative of both maternal and paternal race/ethnicity, we used maternal and paternal race (white, black, other) and ethnicity (e.g., of Hispanic origin, yes or no) data to categorize each parent as NHW, NHB, NHO, and Hispanic (regardless of race). We then combined maternal race/ethnicity and paternal race/ethnicity to generate a parental race/ethnicity variable for each possible parental combination. Because of sparse data concerns regarding some of the possible combinations (e.g., NHW/NHO parental race/ethnicity $n = 2$), we opted to evaluate those categories with an adequate number of subjects, including NHW/NHW, NHW/NHB, NHB/NHB, NHW/Hisp, and Hisp/Hisp parental race/ethnicity combinations.

Statistical analysis

Unconditional logistic regression was used to evaluate the association between various parental and perinatal characteristics obtained from vital records and the risk of the LCH. Each parental or perinatal characteristic of interest served as the exposure in each analysis. First, we generated odds ratios (OR) and 95% confidence intervals (CI) to evaluate the association between each characteristic and LCH, adjusting only for the matching variable: year of birth. We then calculated an adjusted OR (aOR) including other independent variables if they were (a) differentially distributed between cases and controls at $P < .05$ and (b) identified as important predictors of LCH in the literature. These covariates included maternal race/ethnicity (reference = NHW), infant sex (reference = male), and the matching variable birth year. To control for acculturation effects when evaluating the associations between maternal, paternal, and parental race/ethnicity and LCH, we opted to adjust for maternal nativity (reference = United States), residence in one of 14 counties along the United States-Mexico border (reference = no), in addition to infant sex (reference = male), and birth year. When estimating the association between paternal race/ethnicity and LCH risk, we adjusted for those variables included in the maternal and parental race/ethnicity estimations, and additionally adjusted for maternal race/ethnicity (reference = NHW). All analyses were conducted in Stata 13.1 (StataCorp LP, College Station, TX).

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