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Neonatal Vitamin D and Childhood Brain Tumor Risk

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Abstract

Vitamin D deficiency among pregnant women is common. Compelling animal evidence suggests carcinogenic effects of vitamin D deficiency on the brains of offspring; however the impact of circulating vitamin D [25(OH)D] on childhood brain tumor (CBT) risk has not been previously evaluated. Using linked birth-cancer registry data in Washington State, 247 CBT cases (< 15 years at diagnosis; born 1991 or later) were identified. 247 birth year, sex and race-matched controls were selected from the remaining birth certificates. Liquid chromatography-tandem mass spectrometry was used to measure circulating levels of vitamin D_3 [25-(OH)D3] in neonatal dried blood spots. Overall, no significant associations were observed. However, when stratified by median birth weight (3,458 grams), there was evidence of increasing risk of CBT with increasing 25-(OH)D3 among children in the higher birth weight category. Compared to the lowest quartile (2.8-7.7 ng/mL), odds ratios (OR) and 95% Confidence Intervals (CI) for the 2nd (7.7-< 11.0 ng/mL), 3rd (11.0-<14.7 ng/mL) and 4th (14.7-37.0) quartiles of 25-(OH)D3 were 1.7 (1.0-3.3), 2.4 (1.2-4.8) and 2.6 (1.2-5.6), respectively. Among children in the lower birth weight category, there was suggestive evidence of a protective effect: ORs and 95% CI for the 2nd, 3rd and 4th quartiles were 0.9 (0.4-1.9), 0.7 (0.3-1.4) and 0.6 (0.3-1.3), respectively. Any associations of neonatal vitamin D with CBT may be birth weight-specific, suggesting the possible involvement of insulin-like growth factor 1 (IGF-1), circulating levels of which have been associated with vitamin D and accelerated fetal growth.

Keywords

brain cancer; pediatric cancer; vitamin D; birth weight

Introduction

Decreased circulating vitamin D [25-(OH)D] has been associated with increased risks of various adult onset cancers, particularly colorectal cancer[1]; however, no studies of 25-

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(OH)D and risk of childhood cancers have been conducted. 25-(OH)D deficiency during gestational development may be particularly relevant to childhood brain tumor (CBT) risk, since animal studies of prenatal vitamin D depletion have demonstrated increased proliferation and reduced apoptotic cell death in neuronal cells and increased brain size and altered brain shape[2,3]. This negative impact of vitamin D restriction is concerning since recent data suggest that vitamin D deficiency is common among pregnant women[4,5]. For example, in a US study of 494 pregnant women, 41% were vitamin D deficient [25-(OH)D <20 ng/mL] and another 41% were vitamin D insufficient [25-(OH)D = 20-32 ng/mL][5].

To examine the association of gestational levels of 25-(OH)D with risk of CBT, we conducted a case-control study using linked birth certificate and cancer registry data from Washington State in conjunction with archived neonatal dried blood spots (DBS) to generate proxy measures of gestational 25-(OH)D. We also explored potential differential effects of 25-(OH)D by various factors including birth weight, maternal smoking, season of birth and CBT subtypes.

Materials and Methods

Study Subjects

Study procedures were approved by the Washington State and Fred Hutchinson Cancer Research Center Institutional Review Boards. All newly diagnosed CBT cases <15 years old were identified through the Cancer Surveillance System of Western Washington and the Washington State Cancer Registry. Potentially eligible cases, identified by cancer-birth registry linkage, were restricted to those born in Washington State during 1991–2010 since these were the earliest and latest years for which archived DBS and cancer registry data were available, respectively. Controls were selected (1:1) from the remaining birth records, matched to cases on year of birth, race (White, Black, Asian or Other) and sex. Additional information available from the birth records included maternal (age and education at delivery and prenatal smoking) and infant characteristics (gestational length, birth month and birth weight). This information was augmented by linked hospital discharge records for the birth hospitalization. Twins or infants born to mothers receiving transfusions and/or receiving treatment for neonatal jaundice were excluded. A total of 374 CBT cases were identified. Size for gestational age was calculated by evaluating the 10^{th} and 90^{th} percentile of the birth weight distribution of Washington State (1989 – 2009) for each week of gestational age, and classified as small for gestational age (SGA; birth weights $\leq 10^{th}$ percentile), appropriate for gestational age (AGA; birth weights between 10^{th} and 90^{th} percentiles) or large for gestational age (LGA; birth weights $\geq 90^{th}$ percentile).

A list of 374 case/control pairs, prioritized for inclusion by histology, was submitted to the Newborn Screening Archives. Primitive neuroectodermal tumors (PNET) (ICD-O-3: 9470, 9471, 9473, 9474) and ependymomas (ICD-O-3: 9391, 9392) were first targeted for inclusion. Astrocytomas were prioritized by histological subtype (high to low priority) as follows: aniplastic astrocytoma (ICD-O-3: 9401), glioblastoma NOS (ICD-O-3: 9440), giant cell glioblastoma (ICD-O-3: 9441), malignant glioma (ICD-O-3: 9380), fibrillary astrocytoma (ICD-O-3: 9420), astrocytoma NOS (ICD-O-3: 9400), pleomorphic astrocytoma (ICD-O-3: 9424) and pilocytic astrocytoma (ICD-O-3: 9421). If a DBS could

not be obtained for either a case or the matched control, both subjects were excluded and the next case/control pair was considered on the list until a total of 250 case/control pairs had been selected.

Neonatal Dried Blood Spots

Neonatal DBS are stored at room temperature by the Newborn Screening Archives for 21 years. From the first 250 case/control pairs for which DBS were successfully located, archive staff removed a 6.35mm punch from the center of a fully saturated DBS and placed the punch in a wax sample bag for delivery to the measurement laboratory. Before release, specimens were anonymized by staff using a previously described protocol[6]. Punches were also taken from five finger stick dried blood spots that were collected from each of five healthy adult volunteers (n=25 DBS) and randomly distributed among study samples for quality control assurance.

Vitamin D Measurements

25(OH)D2 and 25(OH)D3 were measured in DBS using liquid chromatography/tandem mass spectrometry (LC-MS/MS) by ZRT Laboratory (Beaverton, OR)[7,8]. Levels of 25(OH)D2 and 25(OH)D3 in the blood spots were adjusted to equivalent serum levels using an equation derived from a previous analysis of vitamin D from six matched pairs of finger stick blood spots and venipuncture serum samples collected from healthy volunteers[7]. 25(OH)D2 was detected in 8% of the study samples, so only 25(OH)D3, which was detected in 98% of the samples, was considered for further analysis [limit of detection (LOD) for 25(OH)D2 and 25(OH)D3 was 4ng/mL]. For those samples with 25(OH)D3 below the LOD, a value of 2.83 (LOD/$\sqrt{2}$) was assigned [9]. In the QC samples, 25(OH)D3 ranged from 6.9 ng/mL to 47.5 ng/mL. The intra-assay (within person) coefficient of variation (CV) was 8% while the inter-assay (between person) CV was 44%, demonstrating sufficient repeatability of the LC/MS measurements.

Statistical Analyses

Odds ratio (OR) estimates of the relative risk and 95% confidence intervals (CI) were calculated using logistic regression (conditional on year of birth, race and sex) to evaluate the association of 25(OH)D3 [categorical variable with cut points based on approximate quartiles of the 25(OH)D3 distribution among controls] with CBT (Stata, V.13.0, College Station, Texas). Statistical significance ($p < 0.05$) was based on Wald tests of the 25(OH)D3 parameter estimates. Trends were assessed by examining p-values for the association of continuous 25(OH)D3 and CBT risk. Categorical variables for birth weight, gestational age, size for gestational age, maternal smoking during pregnancy, maternal education, maternal age at delivery and season of birth (determined from birth month) were evaluated as potential confounders. Potentially modifying effects of these variables on the 25(OH)D3 and CBT association were evaluated by conducting likelihood ratio tests on nested models containing main effect and cross-product terms for each variable. CBT subtype-specific analyses for the major histological categories (astrocytoma, ependymoma and PNET) and age at diagnosis (< 5 years of age and ≥5 years of age) were also conducted.

Results

From the prioritized roster of 374 case/control pairs, DBS for 65 case/control pairs were not searched for because the quota of 250 case/control pairs had been reached. DBS were not obtained for 59 case/control pairs because the DBS for either the matched case or control: 1) was collected more than 48 hours after delivery (50%); 2) could not be located in the archives (29%); 3) was not stored in the archives because the corresponding birth occurred at a military hospital (12%); or 4) was missing a collection date (9%). No significant differences in birth characteristics were found between the subjects for whom DBS were and were not obtained (results not shown). The DBS successfully located for 250 case/control pairs were delivered to the analysis laboratory; however, a handling error resulted in mislabelling of 3 samples, giving a final sample size of 247 case/control pairs.

Mothers of cases were generally younger at delivery and slightly less likely to have reported smoking during pregnancy than mothers of controls. Cases also tended to have higher birth weights and were less likely to be born in fall months than controls (Table 1). Mean (standard deviation) 25(OH)D3 in controls was 11.6 ng/mL (5.2) and in cases was 12.0 ng/mL (5.2). In the regression models, adjustment for potentially confounding variables had minimal impact on the 25(OH)D3 point estimates, so these variables were not included in the final analyses. There was little evidence of a significant overall association between CBT and circulating levels of neonatal 25(OH)D3 (Table 2), and no differences were observed when stratifying by sex, race, gestational age, maternal smoking, maternal age at delivery, season of birth, age at diagnosis and major histological type (results not shown). However, when stratifying by median birth weight among controls, significant effect modification was observed ($p=0.04$) (Table 3). Among cases and controls in the higher birth weight category (3458-4847 grams), ORs were increased in each of the three highest categories of neonatal 25(OH)D3, with evidence of a trend of increasing CBT risk with increasing levels of 25(OH)D3 ($p=0.04$). Among the lower birth weight category (1105-<3458 grams), no statistically significant effects were observed, though there was suggestion of a trend of decreasing CBT risk with increasing 25(OH)D3 ($p=0.4$). The mean level of 25(OH)D3 for the lower and higher categories of birth weight among controls was 12.3 and 11.0 ng/mL, respectively. While there was no statistically significant evidence for effect modification when stratifying by tertiles of birth weight and size for gestational age, the general patterns of reduced risks with increasing 25(OH)D3 among the lowest tertile and SGA categories and increased risks with increasing 25(OH)D3 in the highest tertile and LGA categories were apparent (results not shown).

Discussion

To our knowledge, this is the first study to consider the impact of early life vitamin D on CBT risk. In exploratory analyses, we observed a differential effect of 25(OH)D3 on CBT risk by birth weight. Contrary to our hypothesis, we observed significantly increased risks of CBT with increased levels of neonatal 25(OH)D3 among children in the higher birth weight category. There was suggestive evidence of the expected protective effect of 25(OH)D3 on CBT risk among children in the lower birth weight category.

The observed impact of birth weight may be related to the insulin-like growth factor pathway, which plays a critical role in fetal development, including promoting the proliferation of brain cells[10]. Increased levels of insulin-like growth factor 1 (IGF-1) and its primary binding protein, IGFBP-3, have been associated with increased cancer risk in adults[11]. Although neonatal levels of IGF-1 and IGFBP-3 have not been evaluated in association with childhood cancer risk, greater levels of IGF-1 are thought to be responsible for the observed associations between higher birth weight and increased childhood cancer risk[12]. Several studies have demonstrated correlations between circulating levels of vitamin D and IGF-1 in adults[13–16], and vitamin D supplementation has been observed to increase IGF-1 levels in children[17,18]. Thus, among higher birth weight children, there may be a higher background level of IGF-1 to which increased vitamin D may further contribute, causing IGF-1 levels to surpass a threshold that leads to an increased CBT risk. Among lower birth weights, the contribution of vitamin D to IGF-1 levels may be less critical given that background levels of IGF-1 are likely to be lower. In these circumstances, the anti-cancer effects of vitamin D, such as transcriptional activation of genes that block cell cycle progression[19], may predominate.

25(OH)D3 levels in our study were generally comparable to those observed in other neonatal populations[20,21], though average levels were well below the level of 20ng/mL recommended for children by the American Academy of Paediatrics. In fact, for children of higher birth weights, increased ORs for CBT were observed at 25(OH)D3 levels that were below this limit. Neonatal DBS are collected shortly after birth, so 25(OH)D3 levels in the DBS are likely to reflect *in utero* levels towards the end of pregnancy and, as such, may not be representative of other gestational time periods. Although we did not have data on 25(OH)D3 levels during early pregnancy or for other time points during childhood, in terms of CBT risk, 25(OH)D3 levels during the end of pregnancy may be particularly important since rapid brain development occurs during this time period[22].

Given the small sample size, power to detect effect modification or to identify subtype-specific associations was limited; true differences by these factors may have been missed. Among controls, there was indication of increasing 25(OH)D3 with more recent birth years [e.g. mean 25(OH)D3 from 1991 – 1999 and 2000 – 2010 was 11.1 ng/mL and 12.8 ng/mL, respectively]. This may indicate degradation of 25(OH)D3 in DBS over time, but this was not observed in a previous study evaluating the validity of 25(OH)D3 measurements in similarly archived DBS[23]. Behavioral changes over time, such as increased use of nutritional supplements among pregnant women, may also account for the observed differences in 25(OH)D3. Since cases and controls were matched on year of birth, any systemic differences in 25(OH)D3 by year of birth were unlikely to bias our results. Strengths of the study include population-based identification of cases and controls and use of population-based pre-diagnostic specimens with which we were able to generate quantitative measurements of 25(OH)D3.

Vitamin D deficiency during pregnancy is receiving increased attention, and has been associated with important complications including gestational diabetes and pre-eclampsia[24], suggesting the need for supplementation. The role of vitamin D, however, is complex, and our results, which should be confirmed in future large-scale studies that also can assess the

potential role of IGF-1 to help elucidate possible underlying mechanisms, suggest that it may be difficult to predict the potential impact of vitamin D supplementation in pregnant women.

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Novelty and Impact Statement

This is one of the first evaluations of neonatal circulating levels of vitamin D in association with childhood brain tumor risk. Results warrant additional studies with a detailed examination of the role of birth weight and the potential impact of insulin-like growth factor 1.

Table 1

Maternal and Infant Characteristics of Childhood Brain Tumor Cases and Matched Controls born in Washington State, 1991–2010

	Cases N (%)	Controls N (%)
Maternal Characteristics		
Maternal Smoking During Pregnancy		
No	214 (87)	198 (80)
Yes	31 (13)	43 (17)
Unknown	2 (<1)	6 (3)
Maternal Education		
0 – 11	45 (18)	50 (20)
12	70 (28)	68 (28)
>12	118 (48)	108 (44)
Unknown	14 (6)	21 (8)
Maternal Age at Delivery		
<20	18 (7)	22 (9)
20–24	69 (28)	50 (20)
25–29	65 (26)	77 (31)
30–34	53 (22)	61 (25)
≥35	42 (17)	37 (15)
Infant Characteristics		
Birth year		
1991–1994	72 (29)	72 (29)
1995–1999	94 (38)	94 (38)
2000–2004	56 (23)	56 (23)
2005–2010	25 (10)	25 (10)
Sex		
Male	120 (49)	120 (49)
Female	127 (51)	127 (51)
Race		
White	184 (74)	184 (74)
Black	9 (4)	9 (4)
Asian	17 (7)	17 (7)
Other	37 (15)	37 (15)
Birthweight (grams)		
1105–<3175	45 (18)	62 (25)
3175–<3458	52 (21)	61 (25)
3458–<3770	76 (31)	63 (25)
3770–4847	74 (30)	61 (25)
Gestational Age (weeks)		
25–38	52 (21)	56 (23)
39	65 (26)	68 (27)

	Cases N (%)	Controls N (%)
≥40	129 (52)	123 (50)
Unknown	1 (<1)	0 (0)
Size for Gestational Age		
Small	14 (6)	23 (9)
Appropriate	194 (79)	197 (80)
Large	38 (15)	27 (11)
Unknown	1 (<1)	0 (0)
Season of birth[a]		
Winter	65 (26)	54 (22)
Spring	61 (25)	67 (27)
Summer	59 (24)	46 (19)
Fall	62 (25)	80 (32)
Disease Characteristics		
Age at CBT Diagnosis		
<5	123 (50)	
≥5	124 (50)	
Histological Type		
PNET	55 (22)	
Ependymoma	22 (9)	
Astrocytoma	170 (69)	
Aniplastic	2 (<1)	
Glioblastoma NOS	6 (2)	
Malignant Glioma	77 (31)	
Fibrillary Astrocytoma	4 (2)	
Astrocytoma NOS	16 (7)	
Pleomorphic	6 (2)	
Pilocytic	59 (24)	

[a] Winter = December, January, February; Spring = March, April, May; Summer = June, July, August; Fall = September, October, November

Table 2

Vitamin D and Childhood Brain Tumor Risk

25(OH)D3 (ng/mL)	Cases N (%)	Controls N (%)	Odds Ratio (95% CI)
2.8 – 7.7	48 (19)	61 (25)	1.0 (Ref.)
7.7 – <11.0	65 (26)	61 (25)	1.3 (0.8–2.1)
11.0 – <14.7	71 (29)	63 (25)	1.4 (1.0–2.2)
14.7 – 37.0	63 (26)	62 (25)	1.3 (0.8–2.2)

Table 3

Vitamin D and Childhood Brain Tumor Risk by Birth Weight

25(OH)D3 (ng/mL)	Birth weight[a] (grams)					
	1105 – <3458			3458 – 4847		
	Cases N (%)	Controls N (%)	Odds Ratio (95% CI)	Cases N (%)	Controls N (%)	Odds Ratio (95% CI)
2.8 – 7.7	25 (26)	24 (20)	1.0 (Ref.)	23 (15)	37 (30)	1.0 (Ref.)
7.7 – <11.0	27 (28)	30 (24)	0.9 (0.4–1.9)	38 (25)	31 (25)	1.7 (1.0–3.3)
11.0 – <14.7	21 (22)	31 (25)	0.7 (0.3–1.4)	50 (33)	32 (26)	2.4 (1.2–4.8)
14.7 – 37.0	24 (25)	38 (31)	0.6 (0.3–1.3)	39 (26)	24 (19)	2.6 (1.2–5.6)

[*] Likelihood ratio test for modification of 25(OH)D3 association with CBT by birth weight, p = 0.04

[a] Birth weight stratified at median among controls