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Peri-gestational risk factors for pediatric brain tumors in Neurofibromatosis Type 1

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Abstract

Background—Individuals with Neurofibromatosis Type 1 (NF1) are strongly predisposed to developing pediatric brain tumors (PBTs), especially optic pathway gliomas (OPGs). Although developmental factors have been implicated in the origins of PBTs in both human and animal studies, associations between early-life factors and PBTs have not been evaluated in individuals with NF1. Our objective was to evaluate associations between *peri*-gestational characteristics and PBTs in this population.

Methods—We conducted a cross-sectional study, ascertaining questionnaire and medical record data for 606 individuals <18 years old who enrolled in the NF1 Patient Registry Initiative (NPRI) from 6/9/2011–6/29/2015. One hundred eighty-four individuals had reported PBT diagnoses, including 65 who were identified with OPG diagnoses. Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between PBT and OPG diagnoses and *peri*-gestational characteristics (prematurity, birth weight, parental age, plurality, family history of NF1, assisted reproductive technology, maternal vitamin supplementation, and parental smoking).

Results—We observed no significant associations between any of the assessed characteristics and PBTs overall or OPGs with the exception of birth weight. After controlling for potential confounding variables, we observed a significant positive association between birth weight quartile and OPGs with a HR of 3.32 (95% CI 1.39–7.94) for the fourth (3915.5 g) compared to the first (3020 g) quartile (p for trend = 0.001).

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Contribution of authors

Kimberly J. Johnson initiated the study, analyzed and interpreted the data and prepared drafts of the manuscript.

Nancy Zoellner assisted with data collection and contributed critical editorial comments to the manuscript.

David H. Gutmann contributed to study design, data collection and provided written critique and substantive comments on manuscript drafts.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.canep.2016.03.005>.

Conclusions—Consistent with results for PBTs in the general population, these results suggest that higher birth weights increase OPG risk in individuals with NF1.

Keywords

Neurofibromatosis 1; Glioma; Brain neoplasms; Birth weight

1. Introduction

Neurofibromatosis Type 1 (NF1) is a hereditary tumor predisposition syndrome with a recently estimated birth incidence as high as 1 case in 2000 births [1]. NF1 is caused by germline mutations in the *NF1* tumor suppressor gene [2] and is associated with several clinical signs including café-au-lait spots, skinfold freckling, pigmented iris lesions (Lisch nodules), peripheral nerve sheath tumors (neurofibromas), bone abnormalities, learning and behavioral deficits, and increased susceptibility to neoplasms [3].

Although children with NF1 have increased susceptibility to a number of different glioma types, OPGs are most common, affecting ~15–20% of children with this syndrome [4]. Glioma risk factors, and specifically OPGs, in NF1 are not well-defined. A number of studies have reported that individuals with European ancestry are more likely to be diagnosed with an OPG than those with other ancestries [5–10]. In addition, the results of two small studies suggest that children with *NF1* gene mutations occurring toward the 5' end are more likely to develop an OPG [11,12].

In children without NF1, a number of studies have evaluated the role of *peri*-gestational characteristics, those occurring around the time of pregnancy, and pediatric brain tumor (PBT) development. Fairly consistent findings indicate that higher birth weights increase risk [13], while other reports have indicated that prenatal vitamin supplementation reduces PBT risk [14]. Using data from the international NF1 Patient Registry Initiative (NPRI), our objective was to determine whether *peri*-gestational characteristics are associated with PBTs in the NF1 population.

2. Methods

2.1. Study population

The study population was ascertained from individuals who enrolled in the NF1 Patient Registry Initiative (NPRI) (<https://nf1registry.wustl.edu/>) between 6/9/2011 and 6/29/2015. Detailed methods on the registry have been previously published [15–17]. Briefly, following online consent, registrants select an adult or minor questionnaire version, with parents/legal guardians instructed to complete the minor questionnaire version for registrants <18 years of age. Eligibility criteria included completion of the minor questionnaire version, reported age <18 years of age on the questionnaire at the time of registration, and sufficient information on variables included in the analysis. A total of 606 of 749 individuals who completed the minor questionnaire version were eligible for the analysis. The Washington University Institutional Review Board (IRB) approved this study.

2.2. Variables

Study variables were constructed from data reported on the minor questionnaire that consists of 11 sections inquiring about basic demographics, doctor information, birth history, family history, clinical history, asthma, allergy, and autoimmune history, child & family tumor/cancer history, educational, social, & behavioral characteristics, growth & puberty, pregnancy, and participation in future studies. Demographic and *peri*-gestational variables included sex, race, country, highest household education, gestational age at birth (full-term, premature, don't know), birth weight, parental ages at birth, plurality, family history of NF1, assisted reproduction (conceived by artificial insemination or *in vitro* fertilization), maternal vitamin supplementation, and parental smoking. Participants were asked to specify birth weight in either pounds and ounces or kilograms and reported birth weights were converted to grams for analyses. Birth weights <450 or >6500 g were considered implausible and coded as missing. Mothers were asked in a single question if they took prenatal or multivitamins in association with the participant in the year before pregnancy, during the pregnancy, or during breastfeeding and prenatal vitamin use was categorized as any vs. none. Similarly, for parental smoking, we asked if the mother or father of the participant smoked during any of the periods described above and categorized parental smoking as any vs. none.

2.3. Brain tumors

PBTs were defined as those reported as diagnosed <18 years of age. Brain tumor diagnoses were reported through the question: "Has the participant ever been diagnosed with a brain tumor?" with possible responses of 'Yes', 'No', and 'Don't Know'. If 'Yes' was selected, then the respondent was asked to specify the diagnosis age in years. If the diagnosis age was not reported, a PBT diagnosis was inferred if the subject was reported to be <18 years at the time of NPRI participation. The NPRI questionnaire did not specifically ask about brain tumor subtypes, however we identified a subset of participants diagnosed with an OPG subtype (n = 65) through medical records that were acquired and abstracted for brain tumor diagnoses as part of NPRI participation or through a write-in response on the NPRI questionnaire to a question that asked about other cancer/tumor diagnoses in the participant.

2.4. Missing data

Parental smoking and vitamin supplementation questions were added to the questionnaire in February 2013. To capture missing data for these and other variables included in this analysis (birth weight and length, parental age, brain tumor diagnosis, brain tumor age, prenatal vitamins, parental smoking), three separate Qualtrics (<http://www.qualtrics.com/>) surveys were designed that encompassed the major missing data patterns. A total of 228 of the 606 eligible participants with missing data on one or more variables were emailed a survey link on 2/15/2015 with two reminder emails sent on 2/23/2015 and 3/2/2015. Those who did not respond were telephoned by a staff member to attempt to recover missing data through phone survey completion. Of 228 surveys sent to eligible participants by email, missing data was recovered through these methods for 87 participants (~38%). The majority of non-respondents (n = 141) were those who completed the questionnaire prior to the addition of the maternal vitamin and parental smoking questions in February of 2013 (~85%).

2.5. Statistical analysis

All analyses were conducted using Statistical Analysis Software (SAS) version 9.4 (Cary, NC). We used a longitudinal data analysis given that all exposures were present at or before birth and PBT diagnosis information was reported after birth. We employed Cox proportional hazards regression analysis to estimate hazard ratios (HRs) for associations between peri-gestational characteristics and PBTs. Person-time was calculated as the interval between the reported birth date and the PBT diagnosis age in years or the date of the last questionnaire update, whichever came first. Person-time was imputed using the SAS procedure Proc MI with the Markov Chain Monte Carlo single imputation method for individuals with reported brain tumor diagnoses who were missing data on diagnosis age ($n = 7$) and for non-cases (without reported brain tumor diagnoses) with missing data on birth date ($n = 2$). The results from five independent imputations were combined using the MIANALYZE procedure to generate a summary parameter estimate. All models included sex and birth year. We also conducted a non-parametric analysis using the SAS NPARWAY1 procedure to determine if there was an overall statistically significant difference between PBT group birth weight distributions employing the Kruskal-Wallis test. Post-hoc pairwise comparison tests were run using the KW_SAS macro [18] that utilizes Dunn's test to determine specific groups with significantly different birth weight distributions. P-values were considered statistically significant if <0.05 .

3. Results

After exclusions, 606 subjects were included in this study, among which 184 had reported PBTs, including 65 individuals who were identified as having been diagnosed with an OPG. Participants identified with PBT and OPG diagnoses were more likely than non-cases to report being female, White race and being a U.S. resident. A similar percentage of cases and non-cases had reported highest household education levels Bachelor's degree, while more non-cases had reported highest household education level <High school degree (Table 1).

There were no significant associations between prematurity, maternal age, paternal age, plurality, family history or NF1, prenatal vitamins, maternal smoking or paternal smoking and PBTs or OPGs (Table 2).

After adjusting for birth year, sex, and gestational age category, each 500 g increase in birth weight was associated with a significant 41% increase in the hazard of an OPG diagnosis ($HR = 1.41$, 95% CI 1.14–1.73). The magnitude of the association was smaller and not significant for PBTs ($HR = 1.06$, 95% CI 0.94–1.21). When birth weight was modeled using quartile categories that were created based on the study population's birth weight distribution, we observed positive associations between reported PBTs and birth weight for individuals in quartiles above the first compared to the first quartile with a significant association for the third vs. first quartile ($HR = 1.85$; 95% CI 1.15–2.95). For OPGs, we observed consistent increases in the hazard of an OPG diagnosis with increasing birth weight quartile (p for linear trend = 0.001). Individuals in the fourth (3915.5–5816.5 g) compared to the first (<3020 g) birth weight quartile had a 3.32 fold (95% CI 1.39–7.94) increased hazard of an OPG diagnosis (Table 2). We also ran two models where birth weight was categorized as a binary variable (<4000 and ≥ 4000 g). In the first model that adjusted

for birth year, sex, and gestational age category (don't know, pre-term, and full-term), there was a 40% risk of an OPG diagnosis (HR = 1.39; 95% CI 0.79–2.45). In the second model that adjusted for birth year and sex that was limited to individuals who were reported to be born full-term, there was a 23% increased risk of an OPG diagnosis (HR = 1.23; 95% CI 0.70–2.16) (data not shown). Unadjusted results for all variables shown in Table 2 were similar to those in Table 2 (Supplementary Table 1).

To further explore the association between higher birth weights and PBT development, we examined the birth weight distributions of those reported to have been diagnosed with PBTs unspecified (excluding known OPGs) and OPGs specifically and those without reported PBT diagnoses. The birth weight distributions were significantly different between groups with medians for the no PBT, PBT unspecified, and OPG groups of 3446.6, 3461.5, and 3745.4 g, respectively (Fig. 1, panel A). We also conducted a more stringent analysis to reduce the effect of potential confounding by gestational age and outlier birth weights that was limited to those who were reported to have been born full-term at birth weights between 2922.5 g (10th percentile) and 4312.8 g (90th percentile) (Fig. 1, panel B). The birth weight distributions remained significantly different between groups with medians for the no PBT, PBT unspecified, and OPG groups of 3574.9, 3518.2 and 3745.4 g, respectively. The post-hoc Dunn test rejected the null hypothesis at $p = 0.05$ for no difference in birth weight distributions between the OPG and PBT unspecified and OPG and no PBT groups but not between the no PBT and PBT unspecified groups.

4. Discussion

This is the first study of *peri*-gestational characteristics and PBT diagnoses in the NF1 population. Overall, we observed that most *peri*-gestational characteristics do not strongly influence PBT or OPG risk in individuals with NF1, with the possible exception of birth weight.

Higher birth weight has frequently been reported as a PBT risk factor in individuals without NF1. Harder et al. reported results from a *meta*-analysis of 8 studies (published in 2003 or earlier) that examined associations between birth weight and astrocytomas. The authors reported a summary OR of 1.38 (95% CI 1.07–1.79) for individuals with birth weights >4000 versus ≤4000 g [13]. A population-based Swedish registry linkage study also examined associations between birth weight and astrocytoma subtypes in individuals whose brain tumors were diagnosed in childhood through younger adulthood (< 38 years), finding that individuals with birth weights >4000 versus 2500–3999 g had a significant increased risk for pilocytic astrocytomas specifically, but not for other astrocytomas, medulloblastomas, or ependymomas [19]. These results are consistent with our findings for NF1-OPGs, a glial neoplasm classified as a pilocytic astrocytoma of the optic nerve, chiasm, or tract [20]. Finally, a 2013 study provided some evidence for positive associations between higher birth weights and large size for gestational age and childhood gliomas [21], while a 2014 study did not find an association [22].

It is of interest to note that we did not find an association between PBTs overall and birthweight. We can think of two possible explanations for this discrepancy. First, it is

possible that the etiology for different glioma subtypes diagnosed in children with NF1 is different. Since PBTs likely represent a heterogeneous class of brain tumor types, any signal from OPGs within the PBT category may have been masked if the birth weight association is specific for OPGs. Second, OPG diagnoses were largely ascertained from medical records that were received for subjects in the study, which could result in relatively higher reporting accuracy than PBTs overall. If there is a greater potential for non-differential misclassification of PBTs than OPGs due to the ascertainment method, the most likely effect of this misclassification would be to bias parameter estimates toward the null.

A potential biological mechanism for the association between higher birth weights and PBTs has been hypothesized to reflect the effects of higher exposure to insulin-like growth factor 1 (IGF-1) [13]. IGF-1 is a hormone that is critically important in growth and development, such that genetic deletion of *Igf-1* in mice results in viable pups with lower birth weights [23]. In addition, higher cord blood IGF-1 levels have been positively associated with birth weight [24,25]. Relevant to brain tumors, IGF-1 is required for normal central nervous system development [26], where IGF-1 has been shown to increase malignant glioma cell proliferation *in vitro* [27]. Moreover, treatment with an IGF-1 receptor inhibitor reduced glioma tumor growth, survival, and migration [28]. In addition, the IGF-1 receptor is a receptor tyrosine kinase that activates the RAS pathway [29], that neurofibromin (the protein product of the *NF1* gene) negatively regulates. While formal mechanistic studies are required, these epidemiological findings suggest that higher birth weights could be a marker of higher *in utero* IGF-1 exposure, which could increase the growth of putative OPG cells of origin to increase the risk of glioma formation.

We did not find evidence for strong links between any of the other *peri*-gestational factors and PBT development, although we note that the percentage of individuals who were reported to have been conceived by assisted reproductive technology was too small to make conclusions. Parental age (either maternal or paternal) has been positively linked to PBTs in some large studies [30–32], although the risk estimates are relatively small. Previous studies do not suggest that plurality is related to PBT risk [22,33]. A *meta*-analysis that included a total of 25 cohort and case-control studies found that children who were born after fertility treatment had a pooled increased risk of 1.88 (95% CI 1.02–3.46) for central nervous system/neural cancers compared to those who were not born after fertility treatment exposure [34].

Relatively consistent evidence for an inverse association between prenatal vitamin supplementation and PBTs in the general population has been reported (reviewed in Johnson et al. [14]), which is consistent with our finding for PBTs but not for OPGs specifically. Our finding of no association between parental smoking and offspring PBTs/OPGs is in agreement with evidence from studies of PBTs in children without NF1 [14,35,36].

As with all observational studies, our study has both strengths and limitations. A major strength of this study is its large size. In addition, because all participants have a serious disease, our study design may be less susceptible to reporting differences between case and non-case (control) parent/legal guardian than other observational studies that include healthy

controls. This limits concern about systematic bias of risk estimates due to differential misclassification of exposures between cases and non-cases.

Chief limitations of our study include a non-population-based sample of individuals with NF1, respondent-reported data accuracy, and missing data on some variables. Currently, it is difficult if not impossible to obtain a population-based sample of individuals with rare diseases in most geographic locations with the possible exception of Nordic countries [1]. Although it is impossible to determine the extent to which individuals who participated in the registry vary from non-participants for most exposures analyzed due to the lack of population-based data, it seems unlikely that the birth weight distribution of cases and non-cases in our dataset would vary systematically from that of the general population of individuals with NF1. However, given the small number of individuals with OPGs, replication in another sample of individuals with NF1 will be required to validate this finding.

With respect to reporting accuracy, reporting of birth weight has been shown to be reasonably accurate compared to birth records [18,37]. However we note that gestational age was reported as a categorical variable rather than in weeks, which could result in estimates for birth weight associations with residual confounding. Parent-reported parental smoking status has also been shown to be a valid and reliable method of measuring these behaviors during pregnancy using cotinine and carbon monoxide measurements as gold standards [38–40]. One study also suggests that reporting accuracy is high for assisted conception [41]. Another limitation of our study is missing data. Respondents who failed to complete questionnaires comprised ~16% of minor subjects. These individuals tended to only complete the first questionnaire section on demographics and were more likely to report a non-White race and a lower household education level (data not shown). Therefore, our results should only be considered generalizable to individuals with NF1 who have similar characteristics to those who participated in our study. Further work is necessary to confirm these results.

In summary, our study suggests a possible association between higher birth weight and OPGs. There are no established risk factors for OPG development in NF1. Although replication is needed to validate this result, our data could have implications for the development of clinical risk prediction models and for defining the biological mechanisms underlying OPG development in children with NF1.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

NF1	Neurofibromatosis Type 1
NPRI	NF1 Patient Registry Initiative
OPG	optic pathway glioma
PBT	pediatric brain tumor

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Fig. 1.

Birth weight distribution by PBT status. Box plots are shown for all subjects (Panel A) and for individuals who were reported to be born at full-term and between the 10th and 90th percentiles (~2922.5–4312.8 g) (Panel B). The minimum and maximum observations below the $1.5 \times$ the interquartile range respectively are represented by the horizontal whisker lines. Observations outside of the horizontal whiskers are represented by circles (i.e. outliers). The means and medians are denoted by the diamonds and the lines inside the boxes, respectively. The upper and lower edges of the box represent the 75th and 25th percentiles. The number

of subjects contributing to data to Panel A is 422, 119, and 65 and to Panel B is 360, 73, and 45 for the No PBT, PBT unspecified, and OPG groups, respectively.

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Table 1

Demographic and birth characteristics of the NPRI study population.

Variable	Non-cases (n = 422) ^a	PBT cases (n = 184) ^a	OPG cases (n = 65) ^a
Sex–N (%)			
Male	224 (53.1)	84 (45.7)	31 (47.7)
Female	198 (46.9)	100 (54.4)	34 (52.3)
Race–N (%)			
White	331 (78.4)	160 (87.0)	57 (87.7)
Black	18 (4.3)	1 (0.5)	0 (0)
Asian	16 (3.8)	1 (0.5)	0 (0)
Unknown/Other	57 (13.5)	22 (12.0)	8 (12.3)
Residence– N (%)			
USA	343 (82.1)	142 (78.0)	49 (76.6)
Non-USA	75 (17.9)	40 (22.0)	15 (23.4)
Highest household education–N (%)			
< High school degree	15 (3.6)	2 (1.10)	1 (1.6)
High school degree or equivalent	57 (13.6)	24 (13.2)	5 (7.8)
Some college, no degree	65 (15.5)	42 (23.1)	14 (21.9)
Associate, Occupational, or Technical degree	82 (19.5)	30 (16.5)	13 (20.3)
Bachelor's degree	201 (47.9)	84 (46.2)	31 (48.4)
Mean age (sd) at baseline NPRI registration	7.9 (4.4)	9.0 (4.3)	8.2 (4.2)

^aNon-cases, PBTs, OPG missing data: residency (n = 4, 2, 1), household education (n = 2, 2, 1).

Table 2

Cox proportional hazards regression results for associations between *peri*-gestational factors and PBTs and OPGs.^a

Variable	Non-cases N (%)	PBT Cases N (%)	HR ^b	95% CI	OPG Cases N (%)	HR ^b	95% CI
Gestational age							
Full term	349 (84.9)	155 (85.6)	1.00	Ref.	57 (89.1)	1.00	Ref.
<Full term	62 (15.1)	26 (14.4)	0.98	0.65–1.49	7 (10.9)	1.32	0.60–2.90
Maternal age (years)							
<35	315 (76.5)	133 (73.1)	1.00	Ref.	45 (69.2)	1.00	Ref.
35	97 (23.5)	49 (26.9)	1.14	0.82–1.58	20 (30.8)	1.41	0.83–2.38
Paternal age (years)							
<35	230 (57.9)	107 (60.5)	1.00	Ref.	42 (65.6)	1.00	Ref.
35	167 (42.1)	70 (40.0)	0.92	0.68–1.25	22 (34.4)	0.73	0.43–1.23
Plurality							
Singleton	399 (95.7)	177 (96.2)	1.00	Ref.	63 (96.9)	–	–
Multiple	18 (4.3)	7 (3.8)	1.02	0.48–2.17	2 (3.1)	–	–
Family history of NF1							
Yes	144 (34.3)	54 (29.4)	1.00	R Ref.	21 (32.3)	1.00	Ref.
No	241 (57.4)	117 (63.6)	1.36	0.98–1.88	39 (60.0)	1.23	0.72–2.11
Don't Know	35 (8.3)	13 (7.1)	0.95	0.51–1.77	5 (7.7)	0.94	0.33–2.67
Assisted reproductive technology							
Yes	16 (4.1)	3 (1.7)	–	–	1 (1.6)	–	–
No	375 (94.9)	172 (97.7)	–	–	61 (96.8)	–	–
Don't Know	4 (1.0)	1 (0.6)	–	–	1 (1.6)	–	–
Prenatal vitamins							
Any	272 (91.9)	128 (87.7)	0.69	0.42–1.13	48 (92.3)	1.03	0.37–2.86
None	24 (8.1)	18 (12.3)	1.00	Ref.	4 (7.7)	1.00	Ref.
Maternal smoking							
Any	54 (18.5)	35 (25.2)	1.39	0.95–2.05	10 (22.2)	1.10	0.55–2.21
None	238 (81.5)	104 (74.8)	1.00	Ref.	41 (80.4)	1.00	Ref.
Paternal smoking							
Any	73 (25.0)	46 (32.9)	1.33	0.94–1.90	15 (29.4)	1.18	0.65–2.17
None	219 (75.0)	94 (67.1)	1.00	Ref.	36 (70.6)	1.00	Ref.
Birth weight ^c	390	169	1.06	0.94–1.21	61	1.41	1.14–1.73
Birth weight quartile (grams) ^d							
Q1: 567.4–3020	101 (25.9)	34 (20.0)	1.0	Ref.	8 (12.9)	1.00	Ref.
Q2: 3035.8–3489.8	105 (26.9)	43 (25.3)	1.21	0.76–1.94	10 (16.1)	1.24	0.47–3.26
Q3: 3500–3887.1	88 (22.6)	52 (30.6)	1.85	1.15–2.95	19 (30.7)	2.91	1.19–7.08
Q4: 3915.5–5816.5	96 (24.6)	41 (24.1)	1.38	0.85–2.26	25 (40.3)	3.32	1.39–7.94

^aMissing data included those who responded 'Don't Know' to the questions about prematurity, prenatal vitamin supplementation, and parental smoking. Missing data from models on single variables for all groups combined (non-cases, PBT cases, and OPG cases) is as follows: prematurity

n = 13, birth year n = 2, sex n = 0, maternal age n = 10, paternal age n = 30, plurality n = 3, family history of NF1 n = 0, assisted reproductive technology n = 33, prenatal vitamins n = 163, maternal smoking n = 174, paternal smoking n = 173, birth weight n = 41.

^b All models included birth year and sex.

^c HR per 500 g increment, adjusted for birth year, sex, and gestational age category.

^d Adjusted for gestational age category (don't know, full-term, pre-term).

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