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Perinatal and early life risk factors for childhood brain tumors: Is instrument-assisted delivery associated with higher risk?

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Abbreviations: AGA, appropriate for gestational age; CNS, central nervous system; ICCC-3, International Classification for Childhood Cancer – 3rd Edition; ICD-O-3, International Classification for Diseases in Oncology – 3rd Edition; LGA, large for gestational age; NARECHEM-ST, National Registry for Childhood Hematological Malignancies and Solid Tumors; OR, odds ratio; SGA, small for gestational age

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ABSTRACT

Background: The childhood peak of brain tumors suggests that early-life exposures might have a role in their etiology. Hence, we examined in the Greek National Registry for Childhood Hematological Malignancies and Solid tumors (NARECHEM-ST) whether perinatal and early-life risk factors influence the risk of childhood brain tumors.

Methods: In a nationwide case-control study, we included 203 cases (0–14 years) with a diagnosis of brain tumor in NARECHEM-ST (2010–2016) and 406 age-, sex-, and center-matched hospital controls. Information was collected via interviews with the guardians and we analyzed the variables of interest in multivariable conditional logistic regression models.

Results: Instrument-assisted delivery was associated with higher (OR: 7.82, 95%CI: 2.18–28.03), whereas caesarean delivery with lower (OR: 0.67, 95%CI: 0.45-0.99) risk of childhood brain tumors, as compared to spontaneous vaginal delivery. Maternal alcohol consumption during pregnancy (OR: 2.35, 95%CI: 1.45–3.81) and history of living in a farm (OR: 4.98, 2.40–10.32) increased the odds of childhood brain tumors. Conversely, higher birth order was associated with lower risk (OR for 2nd vs. 1st child: 0.60, 95%CI: 0.40-0.89 and OR for 3rd vs. 1st: 0.34, 95%CI: 0.18-0.63). Birth weight, gestational age, parental age, history of infertility, smoking during pregnancy, allergic diseases, and maternal diseases during pregnancy showed no significant associations.

Conclusions: Perinatal and early-life risk factors, and specifically indicators of brain trauma, exposure to toxic agents and immune system maturation, might be involved in the pathogenesis of childhood brain tumors. Larger studies should aim to replicate our findings and examine associations with tumor subtypes.

1. Introduction

Brain and other central nervous system (CNS) tumors (hereby called brain tumors for simplicity) are the most common solid tumor in childhood (0–14 years) and the leading cause of cancer mortality in this age group [1]. Although several studies have shed light to the molecular pathogenesis of brain tumors in the last years [2–4], uncertainty exists regarding risk factors contributing to their etiology. The only well-established causal risk factors for childhood brain tumors include specific genetic syndromes and exposure to ionizing radiation [5]. However, the peak of the disease in childhood indicates perinatal and early-life risk factors, as potential causes of childhood brain tumors [5–8]. Among them, factors that have been associated with the risk of childhood brain tumors in observational epidemiologic studies include birth weight and infant growth [9], early-life exposure to pesticides [10], surrogates of early-life exposure to infections including sibship size, birth order, history of infections, and age at enrollment to kindergarten [11–13], parental age [14], and allergic conditions [15].

However, in the majority of the abovementioned risk factors the results are rather inconsistent across different studies, possibly because of small sample sizes, as well as heterogeneity in study design, examined populations, and assessment of risk factors. Furthermore, most studies do not specifically examine the associations with specific histological subtypes. In particular, potentially modifiable perinatal and early-life risk factors should be further explored. Here, we analyze for the first time, data from the Greek nationwide case-control study initiated in parallel with the international MOBI-KIDS project [16], aiming at exploring associations of perinatal and early-life exposures with brain tumors among children.

2. Material and methods

2.1. Study design

Data for this analysis come from a nationwide multi-center case-control study. During the study period (2010–2016), a total of 466 children (0–14 years) of Greek origin with CNS tumors, as defined by the 3rd Edition of the International Classification for Childhood Cancer (ICCC-3) [17], were registered in the National Registry for Childhood Hematological Malignancies and Solid Tumors (NARECHEM-ST). Tumors of any behavior (malignant or non-malignant) were registered. NARECHEM-ST is a nationwide registry of childhood malignancies in Greece. Details on the registration methods of NARECHEM-ST have been previously described [7] and are also available online (http://narechem.gr/node/24). The guardians of these children were contacted and an informed consent for participation in our case-control study was obtained for 203 brain tumor cases (participation rate 43.6%). Brain tumor cases included in the case-control study did not differ from the nationwide population of childhood brain tumors in terms of age, sex, and tumor topography, but the included sample underrepresented tumors of non-malignant behavior and overrepresented embryonal tumors over astrocytomas and tumors of unspecified histology, as detailed in Supplementary Table 1. Summary data of basic demographic and tumor-specific characteristics of the registry population are further available online (http://narechem.gr/node/9). The primary reasons for non-participation in the case-control study were retrospective registration and loss to follow-up, refusal to participate, and fatal malignancies leading to death within a month after diagnosis. Brain tumors were classified to the 6 diagnostic subgroups of ICCC-3 based on their morphology, behavior, and topography codes of the International Classification for Diseases in Oncology- 3rd Edition (ICD-O-3). Controls were children (0–14 years) hospitalized for acute appendicitis (ICD-10 K35 codes) in the pediatric surgical departments of the collaborating hospital within a period of 12 months after the time point of brain tumor diagnoses in the respective cases and were free of cancer and any major chronic comorbidity. Two controls matched for age (± 6 months), sex, and participating center, were selected for every one of the cases. The refusal rate among controls was minimal (~4%), and in case of refusal the next eligible controls were identified from the records of the department. The study protocol has been approved by the Ethics Committee of the Athens University Medical School.

2.2. Study variables

Upon agreement by the treating physician, the guardians of all eligible study participants were informed of the study objectives and were interviewed in person or through telephone by a trained interviewer. A structured questionnaire was used, which was designed in the context of the MOBI-KIDS study, an international case-control study of brain tumors aiming to explore the role of non-ionizing radiation in brain tumorigenesis [16]. The questionnaire covered a series of putative risk factors including sociodemographic, childhood environment and lifestyle variables, perinatal characteristics, family and own medical history. Specifically, we collected data on maternal education, birth weight, gestational age at birth, maternal and paternal age at birth,

Table 1
Distributions of cases with childhood CNS tumors and controls by study variables.

Variables	Cases (N = 203)		Controls (N = 406)		p-value[a]
	N	%	N	%	
Age (y)					matching
0–4	91	44.8	174	42.9	
5–9	58	28.6	120	29.6	
10–14	54	26.6	112	27.6	
Index child's sex					matching
Male	112	55.2	224	55.2	
Female	91	44.8	182	44.8	
Maternal education					0.15
High school or lower	107	52.7	215	53.0	
Technical school/University or higher	94	46.3	169	41.7	
Missing	2	1.0	22	5.4	
Birth weight (g)					0.10
< 2500	12	5.9	41	10.1	
2500–3999	176	86.7	338	83.3	
≥4000	9	4.4	17	4.2	
Missing	6	3.0	10	2.5	
Gestational age at birth					0.08
Pre-term	17	8.4	51	12.6	
Full-term	184	90.6	332	82.0	
Post-term	2	1.0	4	1.0	
Missing	0	0	18	4.4	
Size for gestational age					0.19
SGA	12	5.9	42	10.3	
AGA	158	77.8	301	74.1	
LGA	27	13.3	58	14.3	
Missing	6	3.0	5	1.2	
Maternal age at birth (years)					0.011
< 25	40	19.7	60	14.8	
25–29	63	31.0	110	27.1	
30–34	63	31.0	134	33.0	
35–39	27	13.3	71	17.5	
≥40	4	2.0	19	4.5	
Missing	6	3.0	12	3.0	
Paternal age at birth (years)					0.34
< 25	14	6.9	29	7.1	
25–29	34	16.8	55	13.6	
30–34	65	32.0	128	31.5	
35–39	50	24.6	100	24.6	
≥40	31	15.3	75	18.5	
Missing	9	4.4	19	4.7	
Delivery mode					< 0.0001
Spontaneous vaginal delivery	104	51.2	194	47.8	
Instrument-assisted vaginal delivery	14	6.9	3	0.7	
Caesarean section	82	40.4	205	50.5	
Missing	3	1.5	4	1.0	
Fertility specialist visit before pregnancy					0.09
Yes	17	8.4	19	4.7	
No	182	89.7	362	89.2	
Missing	4	2.0	25	6.2	
Infection in first two weeks					0.99
Yes	3	1.5	6	1.5	
No	197	97.0	394	97.0	
Missing	3	1.5	6	1.5	
Sibship size					0.26
1	54	26.6	98	24.1	
2	101	49.8	197	48.5	
≥3	48	23.7	111	27.3	
Missing	0	0.0	0	0.0	
Birth order					0.002
1	120	59.1	193	47.5	
2	64	31.5	144	35.5	
≥3	19	9.4	69	17.0	
Missing	0	0.0	0	0.0	
Child's age at kindergarten enrollment (y)					0.34
≤1.5	13	6.4	36	8.9	
> 1.5	176	86.7	353	86.9	
Missing	14	6.9	17	4.2	
Alcohol consumption 3 months before, during, or 3 months after pregnancy					0.0002
Yes	50	24.6	46	11.3	
No	150	73.9	320	78.8	
Missing	3	1.5	40	9.9	

(*continued on next page*)

Table 1 (*continued*)

Variables	Cases (N = 203)		Controls (N = 406)		p-value[a]
	N	%	N	%	
Smoking 3 months before, during, or 3 months after pregnancy					0.92
Yes	75	37.0	151	37.2	
No	121	59.6	244	60.1	
Missing	7	3.5	11	2.7	
History of living in a farm					0.0005
Yes	34	16.8	27	6.6	
No	168	82.8	341	84.0	
Missing	1	0.5	38	9.4	
Pet animals in house					0.35
Yes	46	22.7	106	26.1	
No	156	76.9	297	73.2	
Missing	1	0.5	3	0.7	
History of allergic diseases					0.11
Yes	49	24.1	72	17.7	
No	150	73.9	327	80.5	
Missing	4	2.0	7	1.7	
Hypertension in pregnancy					0.50
Yes	7	3.5	10	2.5	
No	195	96.1	391	96.3	
Missing	1	0.5	5	1.2	
Gestational diabetes					0.62
Yes	11	5.4	26	6.4	
No	191	94.1	375	92.4	
Missing	1	0.5	5	1.2	

[a] p-values were derived from Chi-square test.

delivery mode, history of infertility (defined as visit to fertility specialist before conception), history of infection during the first two weeks of life as recalled by the guardian and after examination of the medical records, birth order, sibship size, age at enrollment to kindergarten, maternal alcohol consumption and smoking in the perinatal period (3 months before pregnancy to 3 months after pregnancy), history of living in a farm, pet animals in house, history of allergic disease as recalled by the guardian and as determined by scanning of medical records (atopic dermatitis, allergic rhinitis, asthma, food allergy, known allergy to environmental or pharmaceutical antigens), hypertension in pregnancy, and gestational diabetes. Delivery mode was categorized as spontaneous vaginal delivery, instrument-assisted vaginal delivery, and caesarean section. Size for gestational age was defined as small (SGA), appropriate (AGA), and large for gestational age (LGA), based on the 10^{th} and 90^{th} percentile of the national growth curves. For 18% and 13% of the cases and controls, respectively, we had no available information on gestational week at birth, but rather on gestational month at birth or a raw classification of gestational age, as pre-term, full-term, or post-term. To classify these cases and controls according to size for gestational age, we considered as gestational week at birth, the median gestational week that the respective gestational month or gestational age crude category corresponded to.

2.3. Statistical analysis

The frequencies or distributions of the study variables were compared between the cases and controls with a Chi-square test. We next designed a series of multivariable logistic regression models for each of the potential risk factors that were associated with brain tumors at a p-value ≤ 0.10 in the unadjusted analyses. Although size for gestational age did not reach a $p \leq 0.10$ in the unadjusted analysis, as both birth weight and gestational age showed such associations, we also designed a logistic regression model for this variable. All models were adjusted for the matching factors (age, sex) and maternal education as an index of socioeconomic status, in addition to a number of available confounding variables that were determined by designing conceptual directed acyclic graphs (Supplementary Figure 1). Specifically, we included in the models only confounders and no mediators or instruments for the examined associations [18]. We further repeated the multivariable analyses for the two most numerous brain tumor subtypes, namely astrocytomas (ICCC-3 diagnostic subgroup IIIb) and embryonal tumors (ICCC-3 diagnostic subgroup IIIc). All analyses were based on conditional logistic regression models. Data were analyzed using the SAS statistical software (SAS v9.4; SAS Institute, Cary, North Carolina, USA).

3. Results

A total of 203 childhood brain tumor cases and 406 age-, sex-, and center-matched controls were included in this study. The majority of the tumors (74%) were of malignant behavior. Intracranial/intraspinal embryonal tumors (ICCC-3 IIIc) and astrocytomas (ICCC-3 IIIb) were the most common diagnostic subtypes corresponding to 34% and 31% of the total brain tumors, respectively. Ependymomas (ICCC-3 IIIa), other specified tumors (ICCC-3 IIIe), and other gliomas (ICCC-3 IIId) represented 12%, 10% and 7% of the cases, respectively, whereas tumors of unspecified histology were only 4% of the cases.

Table 1 presents the distribution of the potential risk factors by case-control status. In the crude comparisons, instrument-assisted delivery, maternal alcohol consumption during pregnancy, and history of living in a farm were more common among childhood brain tumor cases, as compared to controls. On the contrary, increasing maternal age at birth and increasing birth order were inversely associated with brain tumors. Maternal education, birth weight, gestational age at birth, size for gestational age, paternal age at birth, visit to a fertility specialist before pregnancy, history of infection in the first two weeks of life, sibship size, age at kindergarten enrollment, maternal smoking in the peripartum period, presence of a pet animal in house, history of allergic diseases, and hypertension or gestational diabetes during pregnancy were not associated with brain tumors.

The multivariable analysis (Table 2) revealed bidirectional associations for mode of delivery, with instrument-assisted delivery being associated with higher (OR: 7.82, 95%CI: 2.18–28.03) and caesarean delivery with marginally lower (OR: 0.67, 95%CI: 0.45-0.99) risk for childhood brain tumors, as compared to spontaneous vaginal delivery.

Table 2
Multivariable associations of study variables with the risk of childhood (0–14 years) brain tumors.

Variables[a]	Total CNS tumors (N = 203)			Astrocytomas (N = 63)			Embryonal tumors (N = 70)		
	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Birth weight (500-gr increment)	1.15	0.92–1.44	0.23	1.23	0.70–2.18	0.47	0.96	0.67–1.37	0.81
Gestational age (1-week increment)	1.04	0.91–1.19	0.58	0.93	0.65–1.32	0.66	1.08	0.87–1.34	0.50
Size for gestational age									
SGA	0.52	0.24–1.13	0.10	0.51	0.12–2.26	0.37	0.52	0.14–1.89	0.32
AGA	Ref			Ref			Ref		
LGA	0.78	0.42–1.44	0.43	0.67	0.12–3.61	0.64	0.49	0.18–1.35	0.17
Maternal age at birth (5-yr increment)	0.86	0.70–1.05	0.13	0.81	0.54–1.19	0.28	0.98	0.73–1.32	0.89
Delivery mode									
Spontaneous vaginal delivery	Ref			Ref			Ref		
Instrument-assisted vaginal delivery	7.82	2.18–28.03	0.002	5.40	0.99–30.29	0.05	n/a		
Caesarean section	0.67	0.45–0.99	0.04	0.58	0.26–1.30	0.19	0.62	0.31–1.24	0.17
Birth order									
1	Ref			Ref			Ref		
2	0.60	0.40–0.89	0.01	0.57	0.28–1.18	0.13	1.15	0.58–2.28	0.69
≥3	0.34	0.18–0.63	0.0006	0.39	0.12–1.27	0.11	0.72	0.26–2.01	0.53
Fertility specialist visit before pregnancy	1.68	0.83–3.41	0.15	0.63	0.12–3.42	0.32	1.49	0.50–4.41	0.47
Alcohol consumption 3 months before, during, or 3 months after pregnancy	2.35	1.45–3.81	0.0006	10.49	2.93–37.60	0.0003	1.65	0.73–3.71	0.23
History of living in a farm	4.98	2.40–10.32	< 0.0001	5.82	1.43–23.66	0.01	10.88	2.43–48.77	0.002

[a] Only variables associated with brain tumors at a p-value ≤ 0.10 in the univariate analysis (Table 1) were considered in multivariable analyses. For every variable we constructed separate multivariable conditional logistic regression analysis models adjusting for the matching factors (age, sex), maternal education, and a number of other factors, as indicated by directed acyclic graphs (Supplementary Figure 1).

The analysis also showed a higher birth order to be associated with a lower risk for childhood brain tumors in a dose-response pattern (OR for 2nd vs. 1st child: 0.60, 95%CI: 0.40-0.89 and OR for 3rd vs. 1st: 0.34, 95%CI: 0.18-0.63). Furthermore, alcohol consumption during pregnancy and history of living in a farm were associated with 2-fold (OR: 2.35, 95%CI: 1.45–3.81) and 5-fold (OR: 4.98, 2.40–10.32) higher odds for childhood brain tumors, respectively.

Although underpowered, the sub-analyses for the two most common histological subtypes of childhood brain tumors, i.e. astrocytoma (N = 63) and embryonal tumors (N = 70), provided hints that astrocytoma drove the associations identified for birth order, instrument-assisted delivery, and maternal alcohol consumption in pregnancy, whereas the associations of brain tumor risk with history of living in a farm and caesarean section seemed to be similar among the two subtypes.

4. Discussion

In this nationwide case-control study a number of perinatal and early-life risk factors were associated with the risk of childhood brain tumors. Of specific interest is the positive association with instrument-assisted vaginal delivery (OR: 7.82, 95%CI: 2.18–28.03) as contrasted to the inverse association with cesarean delivery (OR: 0.67, 95%CI: 0.45-0.99). Moreover, maternal consumption of alcohol during pregnancy (OR: 2.35, 95%CI: 1.45–3.81) and history of living in a farm (OR: 4.98, 2.40–10.32) were associated with higher risk of childhood brain tumors, whereas higher birth order was associated with lower risk of childhood brain tumors (OR for 2 vs. 1: 0.60, 95%CI: 0.40-0.89 and OR for 3 vs. 1: 0.34, 95%CI: 0.18-0.63).

Our analysis showed that instrument-assisted delivery is associated with higher risk of childhood brain tumors. An older case-control study had also reported that delivery assisted by forceps is associated with a 2.6-fold increased risk of childhood brain tumors [19], but a more recent study examining the association with vacuum extraction found no significant association [20]. Instrument-assisted delivery with the use of either forceps or vacuum extraction is associated with higher risk of brain injury [21,22]. Interestingly, it has been suggested in adults that traumatic brain injury might increase the risk for subsequent glioma [23,24], but this has not been confirmed in larger populations [25]. While this finding is of interest, potential sources of bias related to the case-control study design such as selective recall bias should not be excluded. The inverse association between caesarean section and risk of brain tumors, in contrast to other childhood malignancies [26,27], might indicate a gradient by mode of delivery regarding the possibility of brain trauma, but requires cautious interpretation, as we did not avail data to differentiate between emergency and elective caesarean section.

We found a dose-response association between higher birth order and risk of childhood brain tumors. Previous case-control studies have reported similar results for overall childhood brain tumors [11,28–31] and particularly for astrocytomas [28], and embryonal tumors [29], but this is not consistent in the literature [20,32–36]. Our analysis by tumor subtypes was underpowered but showed that the effect might be specific to astrocytomas. Birth order is traditionally used in epidemiologic studies as a surrogate marker of frequency and timing of exposure to infections in early life [36,37]. Specifically, later-born children are considered to be exposed to a larger burden of infections at an earlier age, as compared to their older siblings [36,37]. Hence, earlier exposure to infections possibly associates with an earlier maturation of the immune system that might act protectively against tumorigenesis [38]. However, other mechanisms including different hormonal exposure of later conceived fetuses [39] and microchimerism [40] might also be involved in the observed association.

History of living in a farm was associated with a 5-fold higher risk of brain tumors, which was consistent for both astrocytomas and embryonal tumors. This finding might be related to exposure to pesticides early in life. A meta-analysis has shown that paternal exposure to pesticides either during pregnancy or early in life after birth is associated with increased risk of childhood brain tumors [41]. Individual studies have further shown that residential use of pesticides is particularly associated with astrocytomas [42] and embryonal tumors [43], which might also relate to the genetically determined capacity of the child to metabolize toxic pesticide substances [44,45]. Pesticides are designed to act in the nervous system and some of them have been shown to be carcinogenic in animal models [5,46]. Alternative explanations could include a lower risk of allergies, socioeconomic disparities, and exposure to animals, but none of these factors were associated with brain tumors in our analysis.

Alcohol consumption was further associated with higher risk of brain tumors. While this finding is in accordance with studies in other childhood neoplasms, including leukemia [47] and neuroblastoma [48], it contradicts the results from a combined analysis of two population-based French studies that showed no evidence of an association [49]. Alcohol consumption might simply be an indicator of other lifestyle choices

during pregnancy which could explain the increase in the risk of brain tumors and possibly also the differences between the two studies.

Finally, our results did not support the associations of birth weight and size for gestational age with the risk of childhood brain tumors, which we recently showed in a meta-analysis, possibly because of restricted statistical power in this analysis [9]. This might relate with the very high proportion of caesarean section deliveries in Greece, which leads to infants born on average at an earlier gestational week than expected and consequently with lower but still appropriate for their gestational age birth weights, as compared to other settings [26,50,51]. Due to compliance with the MOBI-KIDS questionnaire, gestational age could not be precisely determined for all participants, thus possibly leading to misclassifications in size for gestational age, which could attenuate a potentially significant effect. Nevertheless, the size of the adjusted for gestational age effect estimate for birth weight in the current case-control study was comparable to the pooled estimate derived in our meta-analysis [9], albeit not reaching statistical significance due to low power issues.

Among the strengths of this study are: the nationwide coverage based on the registration network of NARECHEM-ST in Greece; the wide range of potential perinatal and early-life risk factors for which we collected data following the protocol designed by the multicenter MOBI-KIDS study; and the availability of two sets of age-, sex-, and center-matched controls for each of the brain tumors cases. On the negative side, despite the nationwide coverage, our analyses were primarily based on the inherently rather small size and were thus underpowered to detect significant signals for several risk factors. This did not allow any meaningful analyses by brain tumor subtypes. Furthermore, there were small differences in tumor characteristics between cases included in the case-control study and those recorded in the nationwide registry during the same the period. The underrepresentation of non-malignant tumors (mainly pilocytic astrocytomas) relates to the relatively short hospitalization of these patients leading to difficulties in recruitment after discharge, whereas tumors of unspecified histology were mainly identified retrospectively during extensive search of alternative sources for completion of registration and were thus not possible to be recruited in the case-control study. Although these differences might introduce selection bias in our case-control study, we believe that the differences are relatively small to affect the results of our association analyses. No biological data were available to more precisely define some of the variables of interest, such as exposure to infections based on serological measurements and genetic variants that may predispose to increased toxicity following exposure to pesticides. Finally, we could not differentiate between emergency and elective cesarean section that have been shown to differentially influence the risk for childhood malignancies.

5. Conclusions

In conclusion, our findings show that instrument-assisted delivery, possibly indicating a delivery-related brain trauma might be associated with higher risk of childhood brain tumors with potential clinical and public health implications. Furthermore, maternal alcohol consumption during pregnancy and history of living in farm were associated with higher risk, as opposed to higher birth order that was associated with lower risk, thus highlighting that early-life exposures including toxic agents and infections might play a role in brain tumorigenesis during childhood. These results should be interpreted with caution, due to power issues and require replication and further investigation in large cohort studies and meta-analyses.

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Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.01.017.

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