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Maternal and Perinatal Factors Associated With Childhood Brain Tumors: A Case-Control Study in Vietnam

Huy Ngoc Pham[1], Robert J. Goldberg[2], Loc Quang Pham[3], Hoa L. Nguyen[2], Dao Anh Pham[4], Linh Thi Thuy Mai[4], Toi Lam Phung[5], Doan Quoc Hung[6,7], He Van Dong[1], and Ha Dai Duong[1,6]

Abstract

Introduction: Brain cancer is the leading cause of cancer-related deaths in children and the majority of childhood brain tumors are diagnosed without determination of their underlying etiology. Little is known about risk factors for childhood brain tumors in Vietnam. The objective of this case-control study was to identify maternal and perinatal factors associated with brain tumors occurring in young Vietnamese children and adolescents.

Methods: We conducted a hospital-based case-control study at Viet Duc University Hospital in Hanoi, Vietnam. Cases consisted of children with brain tumors aged 0-14 years old admitted to the hospital from January 2020 to July 2022 while the controls were age and sex-matched hospitalized children diagnosed with head trauma. Perinatal characteristics were abstracted from hospital medical records and maternal medical, behavioral, and sociodemographic factors were collected through in-person interviews. Conditional logistic regression models were used to examine maternal and perinatal factors associated with childhood brain tumors.

Results: The study sample included 220 children (110 cases and 110 controls) whose average age was 8.9 years and 41.8% were girls. Children born to mothers aged greater than 30 years at the time of the child's birth had a higher risk of childhood brain tumors compared to those born to mothers aged from 18 to 30 years old (OR = 2.55; 95% CI: 1.13-5.75). Additionally low maternal body mass index prior to the current pregnancy of <18.5 kg/m^2 significantly increased the odds of having a child with a brain tumor in relation to normal maternal body mass index from 18.5-22.9 kg/m^2 (OR = 3.19; 95% CI: 1.36 - 7.50).

Conclusion: Advanced maternal age and being markedly underweight were associated with an increased odds of having a child with a brain tumor. A population-based study with larger sample size is needed to confirm and extend the present findings.

Keywords

childhood brain tumors, maternal and perinatal risk factors, case-control study, Vietnam

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[1]Department of Neurosurgery, Viet Duc University Hospital, Hanoi, Vietnam
[2]Department of Population and Quantitative Health Sciences, University of Massachusetts Chan Medical School, Worcester, MA, USA
[3]Department of Epidemiology, School of Public Health and Preventive Medicine, Hanoi Medical University, Hanoi, Vietnam
[4]Department of Internal Medicine, Hanoi Medical University, Hanoi, Vietnam
[5]Health Strategy and Policy Institute, Ministry of Health, Hanoi, Vietnam
[6]Department of Surgery, Hanoi Medical University, Hanoi, Vietnam
[7]Department of Cardiovascular and Thoracic Surgery, Viet Duc University Hospital, Hanoi, Vietnam

Corresponding Author:
Huy Ngoc Pham, Department of Neurosurgery, Viet Duc University Hospital, 40 Trang Thi, Hanoi 100000, Vietnam.
Email: doxpham@gmail.com

Introduction

Cancer is the second leading cause of death after cardiovascular diseases and accounts for a fifth of mortality in Vietnam.[1] According to the GLOBOCAN 2022 database, an estimated 2829 new cases were diagnosed of and 2431 deaths were caused by cancers of the central nervous system in Vietnam in 2022 which made them rank 14th in incidence and 11th in terms of cancer-related deaths.[2] Unfortunately, little data is available on the epidemiology of brain tumors for Vietnamese children. Globally, the central nervous system is one of the most common cancer sites in children[3-5] with average annual age-adjusted incidence rates ranging from 1.1 to 6.0 per 100,000 children.[5-7] The most common histological subtypes of childhood brain tumors include gliomas, tumors of the pituitary gland, neuronal-glial tumors, and medulloblastomas with a slight predilection for boys.[5,8] The overall 5-year relative survival rate of children with brain tumors is approximately 75% but varies significantly by tumor site, histological subtype and grade.[5,9] In the United States, with a mortality rate of .66 per 100,000 children annually,[10] brain tumors are associated with more deaths than any other type of childhood cancer.[11,12] The majority of childhood brain tumors are, however, diagnosed without determination of their underlying etiology.

Childhood brain tumors have been associated with a number of genetic disorders, including neurofibromatosis and tuberous sclerosis. However, these uncommon genetic disorders are responsible for less than 5% of brain tumors in children.[13] Several studies have shown that history of allergic conditions such as asthma, hay fever leads to reduced glioma and meningioma risk in adults.[14-16] However, the protective effect conferred by allergy has not been demonstrated for childhood brain tumors in a large pooled data analysis.[17] Ionizing radiation is the only well-established environmental cause of childhood brain tumors, though there is little evidence that low doses of radiation from diagnostic X-rays are related to the development of brain tumors.[18,19]

Current knowledge suggests that the oncogenesis of childhood brain tumors begins during the early stages of embryonic development.[20] While the effects of pregnancy, perinatal, and maternal factors on the development of childhood brain tumors have been examined in a number of studies, the results of these investigations have been mixed. Two meta-analyses found an increased risk of astrocytoma and embryonal tumors in children born with high birth weight[21,22] while no such association was found in 2 case-control studies in France.[23] Advanced maternal age at childbirth was associated with an increased risk of childhood brain tumors in 2 [24,25] large studies in the United States but a population-based study in Germany and a cohort study in Norway failed to confirm this association.[26,27]

Breastfeeding has been shown to have a protective effect for childhood brain tumors in a British case-control study in which there was higher prevalence of breastfeeding in controls than in cases.[28] Meanwhile, in a pooled-data analysis of ten studies conducted across Europe and North America between 1974 and 2019 with a total of 2610 cases and 8128 controls, the association between breastfeeding, even with a duration greater than 6 months, and the likelihood of developing childhood brain tumors was not observed.[29] Performance of a cesarean section, when compared to a vaginal delivery, has been linked to an increased probability of childhood brain tumors in a large systematic review and meta-analysis,[30] a finding in contrast to a multi-national case-control study carried out in Europe.[31] Another study in Denmark reported a higher risk of ependymoma in children with vacuum-assisted deliveries than ones with spontaneous vaginal birth but when combined all types of brain tumors, no effect of either vacuum or forceps deliveries was found.[32]

To our knowledge, no study to date has investigated the risk factors for childhood brain tumors in Vietnamese children and adolescents. This observational study aimed to examine the role of perinatal and maternal factors on the odds of developing brain tumors among Vietnamese children and adolescents.

Methods

The reporting of this study conforms to STROBE guidelines.[33]

Design and Setting

The present investigation was a hospital-based case-control study. Pediatric patients hospitalized at the Department of Neurosurgery, Viet Duc University Hospital (Hanoi, Vietnam) from January 2020 to July 2022 comprised the study population.

Study Population

The cases consisted of children aged 0 to 14 years old who were diagnosed with a brain tumor based on histopathological findings.[34] Controls, who were individually matched to the cases on the basis of sex and age (+/− 1 year), consisted of children admitted to the hospital during the same month as the case who were diagnosed with head trauma without clinical and computed tomography evidence of a brain tumor.

To identify potential participants, study investigators searched the hospital computer system for all pediatric patients hospitalized during the study period. The medical records of children diagnosed with a possible brain tumor, based on International Statistical Classification of Diseases and Related Health Problems 10th Revision[35] coding D32, D33, D35 and C70, C71, C72, C75 categories, were reviewed for study eligibility as possible cases of brain tumor. In a similar manner, the medical records of children diagnosed with head trauma without clinical and computed tomography evidence

of a brain tumor were reviewed for inclusion in the control group. If the child was determined to be eligible for study inclusion, their parents were contacted for their consent and possible study participation.

In both the case and control groups, we excluded children whose parents had neurocognitive or mental health problems based on family history data obtained from hospital medical records and those whose parents declined to participate in the study.

Data Collection

A data collection form was used for abstracting pertinent information from hospital medical records by trained research physicians. The mothers of all study participants were interviewed in person by study physicians based on the use of a questionnaire, which asked about a variety of maternal characteristics. Since few prior studies have found an association between paternal characteristics and the occurrence of childhood brain tumors, data from the children's fathers were not collected. All data collection forms were developed by the study and pilot-tested with ten participants to correct problems regarding language and cultural aspects before being used in the field. Study data was collected from January to May, 2023.

Information was collected about a variety of perinatal and maternal medical, behavioral, and sociodemographic factors possibly related to brain tumors.

The general characteristics of the study population included the child's age at the time of hospital admission, their ethnicity (Kinh, minorities), sex, the residential location (urban, suburban, rural), tumor subtypes according to the 2016 WHO Classification of Tumors of the Central Nervous System,[34] and the tumor location (supratentorial, infratentorial) for the cases.

Regarding maternal factors we examined the age at the time of the child's birth (≤30, >30 years old), medical history (eg, neurological diseases, genetic disorders), obstetric history (eg, miscarriages, abortions, contraception control), receipt of assisted reproductive technology, self-reported smoking and alcohol consumption (weekly use within one year before pregnancy), body mass index before their current pregnancy (<18.5, 18.5-22.9, ≥23 kg/m^2), weight gain during pregnancy, calcium, folic acid supplementation during pregnancy, X-ray exposures by undertaking plain radiography or computed tomography during pregnancy, highest level of education completed, marital status at the time of the child's birth, and household income.

The perinatal factors included birth order, gestational age at birth (preterm as <37 weeks, full term as 37 to less than 42 weeks, post-term as ≥42 weeks of gestation from the first day of last menstrual period), fetal presentation, mode of delivery (vaginal or cesarean section), birth weight (<2500 g, 2500-4000 g, >4000 g), history of asphyxia, intensive care unit admission after delivery, possible birth associated defects, length of being breastfed, family history of brain tumor within 3 generations.

Data Analysis

Characteristics of the study population are presented as means and standard deviations for continuous variables and compared between cases and controls using t-tests. The categorical factors are presented as percentages and compared between the 2 principal study groups using chi-square tests.

Conditional logistic regression models were used to examine the association between maternal and perinatal factors and the odds of having a child with a brain tumor. Variables that yielded a *P*-value <.2 in univariate analysis were included in the multivariable adjusted logistic regression model. Results are presented as odd ratios with 95% confidence intervals. Statistical analyses were performed using Stata 15.0 (College Station, TX: StataCorp LP).

Ethical Considerations

This study was approved by the Institutional Review Board at Hanoi Medical University (789/GCN-HĐĐĐNCYSH-ĐHYHN). Written informed consent was provided by the mothers of children who participated in this study.

Results

Study Population Characteristics

A total of 220 patients comprised the study population with 110 in the case group and 110 in the control group (Figure 1). Reflecting the success of matching, the average ages of both cases and controls were similar and 58.2% of cases and controls were boys; the majority of the study population was of Kinh ethnicity (Table 1).

Among the cases, the tumor types included astrocytoma (50.0%), medulloblastoma (17.3%), craniopharyngioma (13.6%), ependymoma (6.4%), germ cell tumors (4.6%), dysembryonic neuroepithelial tumor (3.6%), atypical teratoid/rhabdoid tumor (1.8%), subependymal giant cell astrocytoma (.9%), embryonal tumor with multiple rosettes (.9%), and meningioma (.9%). Approximately 45% of the tumors were classified as benign and 72% of the tumors were located supratentorially.

Maternal and perinatal characteristics of the cases and controls are presented and compared in Table 1. In the univariate analysis, 8 factors yielded *P*-value <.2 and were included in the final multivariable adjusted analysis (Table 2). These factors included maternal age at the time of the child's birth, maternal body mass index before pregnancy, residential location, receipt of calcium and folic acid supplementation during pregnancy, birth order, and birth weight. None of the mothers in the cases or controls reported drinking alcohol, smoking within 1 year before pregnancy or X-ray exposures during pregnancy by undertaking radiography.

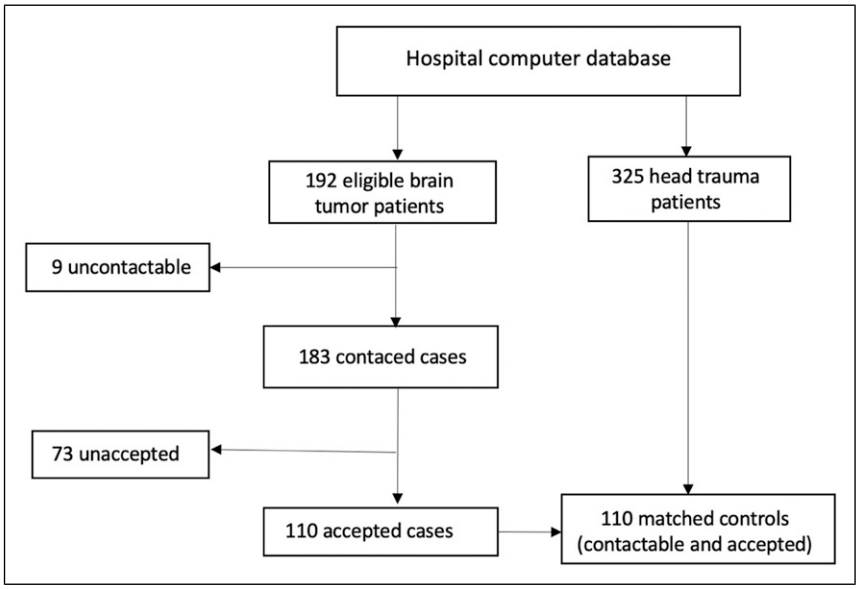

Figure 1. Flow of study participants.

Maternal Characteristics Associated With Childhood Brain Tumors

Children born to mothers greater than 30 years old (OR = 2.55; 95% CI: 1.13-5.75) and mothers who had a low body mass index prior to the current pregnancy (OR = 3.19; 95% CI: 1.36 - 7.50) were associated with significantly increased odds of having a child with a brain tumor (Table 2).

Maternal folic acid supplementation during pregnancy was associated with a decreased likelihood for having a child with a brain tumor in our unadjusted analysis, but the protective effect of folic acid did not remain statistically significant after controlling for several potential confounding variables (Table 2).

Perinatal Characteristics

None of the birth characteristics examined, including birth order, fetal presentation, birth weight, gestational age, or method of delivery were significantly associated with increased odds of having a child with a brain tumor (Tables 1 and 2).

Discussion

We found a statistically significant association between advanced maternal age at the time of childbirth and a low maternal body mass index before their current pregnancy and the odds of their child being diagnosed with a brain tumor.

Maternal Characteristics Associated With Childhood Brain Tumors

We observed a significant increase in the odds of having a child with a brain tumor in children born to mothers of advanced age. In a large population-based study in California with more than 23,000 cases and 87,000 matched controls, advanced maternal age was associated with an increased risk of central nervous system tumors in children. The odds ratio for each 5-year increase in maternal age was 1.08 (95% CI: 1.03-1.13).[25] A large case-control study using pooled population data in the United States also reported an elevated risk of childhood brain tumors with higher maternal age at the time of the child's birth.[24]

Different genetic and physiologic mechanisms have been described to underly this relationship. Advanced maternal age has been associated with an accumulation of mutations at both the chromosome and gene levels in germ cells,[36,37] while degenerative and hormonal changes occur which may adversely affect the female reproductive system as women get older.[38-40]

We found that a low maternal body mass index prior to pregnancy was linked to a higher odds of having a child with a brain tumor. Both a low and a high maternal body mass index prior to a woman's pregnancy has been linked to adverse pregnancy outcomes including preterm labor, abnormal birth weight, and fetal development disorder.[41,42] This association might explain the occurrence of brain tumors in our study because underweight mothers often have a baby delivered of low birth weight.

Little evidence for the link between a low maternal pre-pregnancy body mass index and occurrence of childhood brain tumors has been demonstrated in the literature as previous studies were mostly conducted in developed countries where there was a higher prevalence of women being overweight than underweight. This finding merits further investigation and could have important clinical implications for counseling women in preparing for a pregnancy.

Maternal folic acid supplementation during pregnancy was shown to have a protective effect for childhood brain tumors in

Table 1. Study Population Characteristics.

	Cases (n = 110) n (%)	Controls (n = 110) n (%)	*P*-Value
General demographic characteristics			
Kinh ethnicity	105 (95.4)	107 (97.3)	.47
Diagnosis age (years)[a]			
<1	2 (1.8)	2 (1.8)	
1-5	20 (18.2)	19 (19.0)	
6-10	49 (44.5)	47 (42.7)	
11-14	41 (37.3)	42 (38.2)	
Male[a]	64 (58.2)	64 (58.2)	
Residential location			
Urban	22 (20.0)	20 (18.2)	
Suburban	75 (68.2)	67 (60.9)	.19
Rural	13 (11.8)	23 (20.9)	
Maternal factors			
>30 years old at child's birth	42 (38.2)	19 (17.3)	<.01
Weekly alcohol use within 1 year before pregnancy	5 (4.6)	9 (8.2)	.27
Prior miscarriage or stillbirth before pregnancy	20 (18.2)	22 (20.0)	.73
Prior abortion	24 (21.8)	19 (17.3)	.40
Contraceptive pill use within 1 year before pregnancy	19 (17.3)	22 (20.0)	.60
Use of assisted reproduction technology	2 (1.8)	1 (.9)	.56
BMI before pregnancy (kg/m^2)			
<18.5	28 (25.5)	13 (11.8)	.05
18.5-22.9	70 (63.6)	83 (75.4)	
≥23	12 (10.9)	14 (12.7)	
Weight gain during pregnancy			
<10 kg	48 (43.6)	48 (43.6%)	.48
10-15 kg	40 (36.4)	45 (40.9)	
>15 kg	22 (20)	17 (15.4)	
Calcium supplement use	86 (78.2)	94 (85.4)	.16
Folate supplement use	49 (44.6)	64 (58.2)	.04
Highest education level			
Primary	14 (12.7)	5 (4.6)	
Secondary	43 (39.1)	38 (34.5)	.05
Higher education	53 (48.2)	67 (60.9)	
Being married	107 (97.3)	107 (97.3)	1.00
Household income (US dollars/month) during pregnancy			
<300	65 (59.1)	56 (50.9)	
300-700	37 (33.6)	41 (37.3)	.36
>700	8 (7.3)	13 (11.8)	
Perinatal factors			
Birth order (n,%)			
1	52 (47.3)	67 (60.9)	
2	42 (38.2)	34 (30.9)	
≥3	16 (14.5)	9 (8.2)	.10
Full-term pregnancy	102 (92.7)	104 (94.5)	.58
Vertex presentation	105 (95.5)	104 (94.5)	.76
Vaginal delivery (n, %)	72 (65.5)	78 (70.9)	.38
Birth weight (n, %)			
<2500 g	6 (5.5)	2 (1.8)	
2500 - 4000 g	100 (90.9)	99 (90)	
>4000 g	4 (3.6)	9 (8.2)	.14
Asphyxia or ICU admission after delivery (n, %)	5 (4.5)	4 (3.6)	.73
Birth defect (n, %)	3 (2.7)	1 (.9)	.31
Breastfeeding less than 6 months	30 (27.3)	28 (25.5)	.7601
Family history of brain tumors (n, %)	1 (.9)	2 (1.8)	.56

[a]Matching variables, no comparisons were conducted.

Table 2. Unadjusted and Multivariable Adjusted Odds Ratio of Factors Associated With Childhood Brain Tumors.

	Unadjusted Odds Ratio (95% CI)	Multivariable Adjusted Odds Ratio (95% CI)
Residential location		
Urban	1.00	1.00
Suburban	1.02 (.51-2.03)	.89 (.39-2.02)
Rural	.51 (.20-1.30)	.69 (.22-.17)
Maternal factors		
Age at child's birth		
18-30 years	1.00	1.00
>30 years	2.96 (1.55-5.64)	2.55 (1.13-5.75)
BMI before pregnancy (kg/m2)		
<18.5	2.55 (1.21-5.38)	3.19 (1.36 - 7.50)
18.5-22.9	1.00	1.00
≥ 23	1.02 (.44-2.35)	1.04 (.38 - 2.87)
Calcium supplements during pregnancy		
No	1.00	1.00
Yes	.60 (.30-1.23)	1.09 (.39 - 3.00)
Folate supplementation during pregnancy		
No	1.00	1.00
Yes	.57 (.33-.99)	.73 (.36 - 1.45)
Highest education level		
Primary	2.47 (.80-7.67)	2.12 (.59-7.67)
Secondary	1.00	1.00
Higher education	.69 (.40-1.24)	.59 (.28-1.27)
Perinatal factors		
Birth order (n, %)		
1	1.00	1.00
2	1.59 (.89-2.86)	1.31 (.67-2.53)
>=3	2.29 (.92 - 5.68)	1.38 (.42-4.56)
Birth weight (n, %)		
<2500 g	2.97 (.58-15.24)	4.86 (.77-30.68)
2500-4000 g	1.00	1.00
>4000 g	.44 (.13-1.49)	.35 (.06-2.27)

our unadjusted analyses but was no longer statistically significant in our multivariable adjusted analyses when we controlled for several potentially confounding factors. A large meta-analysis of one cohort and 9 case-control studies showed that maternal folic acid intake was inversely associated with the risk of childhood brain and spinal cord tumors.[43] While the mechanisms underlying this potentially protective effect remain to be clarified, folic acid is essential for nucleotide synthesis and repair. Folic acid deficiency has been shown to be related to an increased risk for chromosomal breakage and inapproriate activation of proto-oncogenes which play a key role in cancer pathogenesis.[44,45]

Perinatal Characteristics Associated With Childhood Brain Tumors

In the present study, we failed to find a statistically significant association between any of the perinatal characteristics examined and the occurrence of brain tumors in children. However, a birth weight of more than 4000 g, or one less than 2500 g, was shown to be related to the development of pediatric brain tumors in a large German population-based study and several meta-analyses.[21,22,26,46] Larger birth size has been associated with a greater number of cells at risk for DNA mutation followed by higher incidence rates of cancer.[47,48] Our result differs from these previous studies which might be due to our relatively small sample size and characteristics of the population under study. A low birth weight is mostly due to preterm delivery which has been shown to be associated with epigenetic alteration,[49,50] that might underly the subsequent development of brain tumors in children. The genetic mutations occurring during the embryonal and fetal stages are associated with the formation cancer stem cells and have been also the subject of studies aiming at early diagnosis and treatment of cancers in adulthood.[51,52]

Study Strengths and Limitations

To our knowledge, this is the first study in Vietnam designed to address risk factors for brain tumors in children and

adolescents. Data collection by both medical record and in-person interview enhanced the accuracy of the information we collected. In this contemporary investigation, the chosen study site is a centrally located public hospital and at the highest level in the healthcare referral system for both head trauma and brain tumors which treats patients from diverse backgrounds from all regions of Vietnam which may improve the generalizability of the study findings. The important limitations of the present study, however, were its relatively small sample size, using hospital-based control group, inability to assess the risk for specific tumor histological subgroups, benign and malignant groups, potential for recall bias on selected possible predisposing factors, and the lack of genetic factor examination.

Conclusions

The results of our hospital-based study suggest that advanced maternal age and being underweight prior to a woman becoming pregnant were associated with an increased odds of their child having a brain tumor. Additional population-based studies of larger sample size remain needed to confirm and extend the present findings, especially in low and middle-income countries.

Appendix

Abbreviations and Acronyms

CBT	Childhood brain tumors
DNA	Deoxyribonucleic acid
OR	Odd ratio
CI	Confidence interval

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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ORCID iD

Huy Ngoc Pham https://orcid.org/0009-0006-6844-9017

Data Availability Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Supplemental Material

Supplemental material for this article is available online.

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