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THE ASSOCIATION BETWEEN BIRTH ORDER, SIBSHIP SIZE, AND GLIOMA DEVELOPMENT IN ADULTHOOD

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Abstract

The etiology of brain tumors is still largely unknown. Previous research indicates that infectious agents and immunological characteristics may influence adult glioma risk. The purpose of our study was to evaluate the effects of birth order and sibship size (total number of siblings), as indicators of the timing and frequency of early life infections, on adult glioma risk using a population of 489 cases and 540 cancer-free controls from the Harris County Brain Tumor Study. Odds ratios for birth order and sibship size were calculated separately from multivariable logistic regression models, adjusting for sex, family history of cancer, education, and age. Each one-unit increase in birth order confers a 13% decreased risk of glioma development in adulthood (OR=0.87, 95% CI=0.79–0.97). However, sibship size was not significantly associated with adult glioma status (OR=0.97, 95% CI=0.91–1.04). Our study indicates that individuals who were more likely to develop common childhood infections at an earlier age (those with a higher birth order) may be more protected against developing glioma in adulthood. More biological and epidemiological research is warranted to clarify the exact mechanisms through which the timing of common childhood infections and the course of early life immune development affect gliomagenesis.

Keywords

glioma; life-course epidemiology; infection; hygiene hypothesis; immune development

INTRODUCTION

Little is currently known about the etiology of brain and other nervous system tumors. The only established risk factors for glioma, which is the most common type of primary brain tumor in adults, are family history and exposure to ionizing radiation.[1,2] These risk factors account for a very small percentage of cases. Although previous studies have suggested that early life viral exposures may play a role in glioma etiology[3–7], consistent evidence of such an association is lacking. Some specific viruses, including polyomaviruses and human cytomegalovirus, have been isolated from brain tumor tissues.[7–11] However, it has also been hypothesized that the timing and frequency of common early life infections may be more important than the presence of a particular virus.[12,13] This hypothesis implies that the impact of the infections on immune system development may have greater influence on the carcinogenic process later in life than cellular effects caused by the presence of the virus. In fact, immunological indicators, such as immunoglobulin E levels and a history of asthma

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and allergies, have been associated with glioma risk[12,14–16], further suggesting that the effect of immune function and development on carcinogenesis warrants additional clarification.

According to the hygiene hypothesis, early life infections can be beneficial to the immune system by promoting a balance between the Th1- and Th2-type immune responses.[17–21] Lack of immunological stimulus early in life is thought to create an imbalance toward Th2-type immunity, which is predominantly responsible for atopic conditions.[18] The timing of exposure is also somewhat correlated with severity of certain viral infections.[21] For example, infections such as mononucleosis or chickenpox tend to be milder when contracted in early childhood rather than in young adulthood.[12,21] Birth order is a frequently used surrogate for the relative timing of exposure to common childhood infections.[12,13,17,20,21] Children who have a higher birth order (i.e. sixth- or seventh-born) are more likely to be exposed to common childhood infections at a younger age, by way of their older siblings.[17,21] Conversely, children with a lower birth order are less likely to be exposed to the same infections until they begin attending school, and thus tend to have a longer period of immunologic isolation early in life, compared to their younger siblings. Similarly, sibship size (number of siblings) can be used as an indicator of the overall frequency of early life infections, as family crowding and intimate contact between larger numbers of children can be correlated with shared exposures to infectious diseases.[12,13] Because obtaining accurate data from adults on the timing and frequency of early life infections is nearly impossible, these surrogate measures can be employed to explore potentially important relationships while eliminating the biases inherent to self-reported data.

The only large population-based study examining the surrogate measures of interest in association with brain tumor etiology was conducted by Altieri et al. using data from the Swedish Family Cancer Database.[12] This study found significant moderate associations between having three or more younger siblings, compared to none, for different types of nervous system tumors. The purpose of our study was to utilize birth order and sibship size to elucidate the impact of the timing and frequency of early life infections on glioma development in adulthood using a population of 489 cases and 540 cancer-free controls from the Harris County Brain Tumor Study.

MATERIAL AND METHODS

Study Population and Data Collection

Cases consisted of adults over the age of 18 years with newly diagnosed, histologically-confirmed glioma (ICD-O-3 codes 9380-9481) identified between January 2001 and January 2006 by hospital physicians in Houston, Texas. Pathology specimens were reviewed by the study neuro-pathologist to confirm glioma diagnosis. Cancer-free controls were obtained through a contracting company by random-digit dialing using standard methods[22,23], and were frequency-matched to cases on age (within five years) and sex. The study population was restricted to non-Hispanic white individuals because we were unable to match on race (due to the small number of minority participants). Eligibility criteria included the ability to speak English. The participation rates for both cases and controls were approximately 80%. Other detailed information on the study population has been reported elsewhere.[24] The study was approved by the M.D. Anderson Cancer Center Institutional Review Board and written informed consent was obtained from all participants.

Structured questionnaires were used to conduct detailed in-person or telephone interviews through which data on demographic factors, health characteristics, and familial attributes were collected. The participants were asked to report their total number of siblings and the dates of birth of immediate family members. The birth order variable was ascertained by

ranking each participant's date of birth compared to their siblings' reported dates of birth. A positive family history of cancer was defined as any self-reported cancer in first-degree relatives (parents, siblings or children).

Statistical Analysis

The distribution of population characteristics was examined by case-control status, using the χ^2 test. The correlation coefficient (Spearman's rho) between sibship size and birth order was examined to determine whether it would be appropriate to include both variables in the same model. The unadjusted associations between total number of siblings, birth order, and glioma status were assessed in separate univariable logistic regression models (SAS PROC LOGISTIC). We also conducted a supplementary analysis in which we constructed a composite variable incorporating both sibship size and birth order (i.e. having more than three younger siblings) to determine if the combination of these two variables would be informative in the logistic regression model.

Covariates that were assessed as potential confounders were based on previous literature and included sex, age at diagnosis, family history of cancer, family history of brain tumor, season of birth, radiation exposure, highest level of education, birth cohort, and maternal age at birth. The final logistic regression models were built using a stepwise method, examining the effect of the addition of each covariate on the parameter estimate of the primary explanatory variable. A 10% change-in-estimate criterion was utilized to determine whether there were data-based confounders in the relationship between each primary explanatory variable and glioma status. If adjustment for a covariate resulted in a less than 10% change in the parameter estimate of the primary explanatory variable, then the decision to keep the covariate in the final model was based on whether adjustment for it was necessary to permit comparison with analyses in previous literature. All statistical analyses were conducted with SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

The characteristics of the study population by case-control status are provided in Table 1. Glioma cases were more likely to have had an education level of high school or less and to report having been exposed to radiation. There were no significant differences between cases and controls with regard to family history of any cancer, season of birth, cigarette smoking status, age, or gender.

Sibship size and birth order were significantly correlated (rho=0.51, p<.0001) in our dataset. Although the two primary explanatory variables were only moderately correlated, birth order does depend on sibship size (for example, one cannot be a fourth-born if one does not have at least three siblings). Because of this interdependence between the variables, we developed separate logistic regression models in order to ensure the statistical integrity and interpretability of the effect estimates. In the univariable logistic regression models, adult glioma status was significantly associated with birth order, but not sibship size (birth order: OR=0.88, 95% CI=0.80-0.97; sibship size: OR=0.97, 95% CI=0.92–1.04).

Table 2 displays the final multivariable models for birth order and sibship size (Panels A and B, respectively). There were no confounders detected based on the 10% change-in-estimate criterion; however, covariates were included in the final models to maintain consistency and allow comparisons with published literature.12 Increasing birth order was inversely associated with the odds of developing glioma in adulthood, adjusting for sex, family history of cancer, education level, birth cohort, and age in years (OR=0.87, 95% CI=0.79–0.97). Sibship size was not significantly associated with adult glioma status, adjusting for the same covariates (OR=0.97, 95% CI=0.91–1.04). Three additional analysis strategies were used to

understand this relationship better (data not shown). First, the logistic regression model including a composite variable of birth order and sibship size (OR=0.96, p-value=0.52) showed no effect. Combining the birth order and sibship size variables appeared to dilute the effect of birth order alone on glioma status, possibly due to the moderate correlation of these two variables (or a lack of adequate power). Second, the possibility of a cohort effect was evaluated by stratifying the final models by birth cohort. The odds ratios for birth order and sibship size remained relatively unchanged across different birth cohorts. Because we found no evidence of a cohort effect, birth cohort was adjusted for in the final model to maintain consistency with previous literature. Finally, we conducted a post-hoc analysis in which we stratified the final model examining birth order by sibship size (≤3 siblings and >3 siblings). The adjusted effect estimates for birth order changed only slightly (for ≤3 siblings stratum: OR=0.89, 95% CI=0.74–1.07; for >3 siblings stratum: OR=0.83, 95% CI=0.71–0.96).

DISCUSSION

In this study, we found that each one-unit increase in birth order confers a 13% decreased odds of glioma development in adulthood (p=0.008). In other words, individuals with a lower birth order (e.g. first- or second-born) have a higher risk of adult glioma development than those with a higher birth order (e.g. fourth- or fifth-born). Sibship size, however, was not found to be associated with adult glioma risk.

A previous study by Wrensch and Barger examined relative birth order and sibship size along with a number of other familial characteristics in relation to glioma risk.25 They found that while cases were likely to have more siblings than controls (p=0.02), they were not differentially the oldest or youngest of their siblings. This study, however, only included male glioma cases and had a small sample size (77 cases and 77 spousal controls).

Altieri et al. examined the association between nervous system tumors and early life viral exposures in a study population of 13,613 nervous system tumor cases from the Swedish Family Cancer Database.12 They used sibship size as a surrogate measure for number of viral exposures in childhood. Using Poisson regression to control for family history of cancer, age, birth cohort, and socioeconomic status, they found significant moderate associations between having three or more younger siblings compared to none for different types of adult and childhood nervous system tumors, including adult hemangioblastoma, ependymoma, and neuroblastoma, and childhood astrocytoma. When examined by relative birth order, they found that these associations were present for having younger siblings, but not older siblings, implying that a longer period of immunologic isolation in early childhood (and a relative postponement of common childhood infections) may be of interest in brain tumor carcinogenesis. Although sibship size proved to be an important risk factor in the Altieri et al. study, our study failed to corroborate their finding. While it is possible that our study had less power to detect a modest association with sibship size, our outcome definition did differ somewhat from that of Altieri et al. in that we considered adult tumors to be those that were diagnosed at age 18 or older. They defined childhood tumors as those that were diagnosed before age 15 and adult tumors as those that were diagnosed after age 15. These differences may account for the discrepancy between the results on the effects of sibship size.

Previous studies have found associations between development of brain tumors and other surrogates of exposure to infectious agents, including seasonal and geographic trends and indicators of maternal infections during pregnancy. 3,6,26–28 Also, several individual viruses have been examined in relation to glioma development. For example, examining the impact of infection with common herpesviruses (i.e. varicella zoster virus, Epstein-Barr virus, and cytomegalovirus) has been of interest.10 According to some studies, having a

history of mononucleosis or chickenpox may confer a protective effect against gliomagenesis.4,5,24

While none of these studies truly separate the cellular effects of the virus itself from the sequelae of the infection on immune system development, they do contribute to our ever-evolving understanding of brain tumor etiology. Since the proposal of the hygiene hypothesis, scientific speculation on the biological mechanism behind these associations has become more focused on the immunological repercussions of the infections and the timing of those infections in childhood rather than the cellular effects of the specific viruses themselves. However, we have yet to discover an accurate and efficient way to study these mechanisms separately.

Our study, the largest case-control study examining the influence of birth order and sibship size on adult glioma status, suggests that individuals who were likely to undergo antigenic challenge at an earlier age (i.e., those with a higher birth order) may be more protected against developing glioma in adulthood. First-born children (those with lower birth order), who likely had the longest period of immunologic isolation in infancy, appear to have the highest risk, relative to those with higher birth order. However, because birth order is only a proxy, we cannot definitively state that the effect observed here is due entirely to the impact of timing of childhood infection on immune development. In fact, birth order is also correlated with other biological factors, such as *in utero* estradiol levels.13 While the use of this surrogate measure constitutes a limitation of our study, there are few other practical methods for determining relative timing of common early life infections. Self-reported timing of infections would likely provide unreliable and incomplete information, as the average person cannot remember such details of their early childhood. Finally, we cannot disregard the possibility that our finding may be an artifact of the structure of our data; thus, these results and our interpretation of them will need to be confirmed in several immunological and epidemiological studies before more definitive conclusions can be drawn regarding the biological relationships at play.

In summary, our study suggests that the timing of early life infections may impact risk of gliomagenesis in adulthood. This is consistent with the fact that other immunological factors, such as history of asthma/allergies or antihistamine use, have also been associated with glioma risk.14–16,24 Studies on glioma etiology conducted to date cumulatively suggest a probable role of immune development and dysfunction in gliomagenesis. However, better measures of immune system development are necessary to corroborate the markers of self-reported infection that are currently being used in epidemiological studies of brain tumor risk.

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References

1. Kleihues, P.; Cavenee, WK. Lyon: International Agency for Research on Cancer (IARC). IARC Press; 2000. Tumours of the nervous system.
2. Bondy ML, Scheurer ME, Malmer B, Barnholtz-Sloan JS, Davis FG, Il'yasova D, Kruchko C, McCarthy BJ, Rajaraman P, Schwartzbaun JA, Sadetzki S, Schlehofer B, et al. Brain tumor epidemiology: consensus from the Brain Tumor Epidemiology Consortium. Cancer. 2008; 113:1953–1968. [PubMed: 18798534]

3. Brenner AV, Linet MS, Shapiro WR, Selker RG, Fine HA, Black PM, Inskip PD. Season of birth and risk of brain tumors in adults. Neurology. 2004; 63:276–281. [PubMed: 15277620]
4. Wrensch M, Weinberg A, Wiencke J, Miike R, Barger G, Kelsey K. Prevalence of antibodies to four herpesviruses among adults with glioma and controls. Am J Epidemiol. 2001; 154:161–165. [PubMed: 11447050]
5. Wrensch M, Weinberg A, Wiencke J, Miike R, Sison J, Wiemels J, Barger G, DeLorenze G, Aldape K, Kelsey K. History of chickenpox and shingles and prevalence of antibodies to varicella-zoster virus and three other herpesviruses among adults with glioma and controls. Am J Epidemiol. 2005; 161:929–938. [PubMed: 15870157]
6. Houben MP, Coebergh JW, Birch JM, Tijssen CC, van Duijin CM, McNally RJ. Space-time clustering patterns of gliomas in The Netherlands suggest an infectious aetiology. Eur J Cancer. 2005; 41:2917–2923. [PubMed: 16274986]
7. Cobbs CS, Harkins L, Samanta M, Gillespie GY, Bharara S, King PH, Nabors LB, Cobbs CG, Britt WJ. Human cytomegalovirus infection and expression in human malignant glioma. Cancer Res. 2002; 62:3347–3350. [PubMed: 12067971]
8. Croul S, Otte J, Khalili K. Brain tumors and polyomaviruses. J Neurovirol. 2003; 9:173–182. [PubMed: 12707848]
9. Del Valle L, Gordon J, Enam S, Delbue S, Croul S, Abraham S, Radhakrishnan S, Assimakopoulou M, Katsetos CD, Khalili K. Expression of human neurotropic polyomavirus JCV late gene product agnoprotein in human medulloblastoma. J Natl Cancer Inst. 2002; 94:267–273. [PubMed: 11854388]
10. Scheurer ME, Bondy ML, Aldape KD, Albrecht T, El-Zein R. Detection of human cytomegalovirus in different histological types of gliomas. Acta Neuropathol. 2008; 116:79–86. [PubMed: 18351367]
11. Mitchell DA, Xie W, Schmittling R, Learn C, Friedman A, McLendon RE, Sampson JH. Sensitive detection of human cytomegalovirus in tumors and peripheral blood of patients diagnosed with glioblastoma. Neuro Oncol. 2008; 10:10–18. [PubMed: 17951512]
12. Altieri A, Castro F, Bermejo JL, Hemminki K. Association between number of siblings and nervous system tumors suggests an infectious etiology. Neurology. 2006; 67:1979–1983. [PubMed: 17159104]
13. Altieri A, Hemminki K. Number of siblings and the risk of solid tumours: a nationwide study. Br J Cancer. 2007:1–5.
14. Wiemels JL, Wiencke JK, Patoka J, Moghadassi M, Chew T, McMillan A, Miike R, Barger G, Wrensch M. Reduced immunoglobulin E and allergy among adults with glioma compared with controls. Cancer Res. 2004; 64:8468–8473. [PubMed: 15548720]
15. Schoemaker MJ, Swerdlow AJ, Hepworth SJ, McKinney PA, van Tongeren M, Muir KR. History of allergies and risk of glioma in adults. Int J Cancer. 2006; 119:2165–2172. [PubMed: 16823851]
16. Schwartzbaum JA, Ahlbom A, Malmer B, Lonn S, Brookes AJ, Doss H, Debinski W, Henriksson R, Feychting M. Polymorphisms associated with asthma are inversely related to glioblastoma multiforme. Cancer Res. 2005; 65:6459–6465. [PubMed: 16024651]
17. Sadovnick AD, Yee IML, Ebers GC. Canadian Collaborative Study Group. Multiple sclerosis and birth order: a longitudinal cohort study. Lancet Neurol. 2005; 4:611–617. [PubMed: 16168929]
18. Karmaus W, Botezan C. Does a higher number of siblings protect against the development of allergy and asthma? J Epidemiol Community Health. 2004; 56:209–221. [PubMed: 11854343]
19. Gibbs S, Surridge H, Adamson R, Cohen B, Bentham G, Reading R. Atopic dermatitis and the hygiene hypothesis: a case-control study. Int J Epidemiol. 2004; 33:100–207. [PubMed: 15075153]
20. Hughes AM, Crouch S, Lightfoot T, Ansell P, Simpson J, Roman E. Eczema, birth order, and infection. Am J Epidemiol. 2008; 167:1182–1187. [PubMed: 18344510]
21. Westergaard T, Andersen PK, Pedersen JB, Olsen JH, Frisch M, Sorensen HT, Wohlfahrt J, Melbye M. Birth characteristics, sibling patterns, and acute leukemia risk in childhood: a population-based cohort study. JNCI. 1997; 89(13):939–947. [PubMed: 9214673]
22. Harlow BL, Davis S. Two one-step methods for household screening and interviewing using random digit dialing. Am J Epidemiol. 1988; 127:857–863. [PubMed: 3354550]

23. Hartge P, Brinton LA, Rosenthal JF, Cahill JI, Hoover RN, Waksberg J. Random digit dialing in selecting a population-based control group. Am J Epidemiol. 1984; 120:825–833. [PubMed: 6334439]

24. Scheurer ME, El-Zein R, Thompson PA, Aldape KD, Levin VA, Gilbert MR, Weinberg JS, Bondy ML. Long-term anti-inflammatory and antihistamine medication use and adult glioma risk. Cancer Epidemiol Biomarkers Prev. 2008; 17:1277–1281. [PubMed: 18483351]

25. Wrensch MR, Barger GR. Familial factors associated with malignant gliomas. Genet Epidemiol. 1990; 7:291–301. [PubMed: 2227374]

26. McCredie M, Maisonneuve P, Boyle P. Perinatal and early postnatal risk factors for malignant brain tumours in New South Wales children. Int J Cancer. 1994; 56:11–15. [PubMed: 8262665]

27. Menegaux F, Olshan AF, Neglia JP, Pollock BH, Bondy ML. Day care, childhood infections, and risk of neuroblastoma. Am J Epidemiol. 2004; 159:843–851. [PubMed: 15105177]

28. McNally RJ, Cairns DP, Eden OB, Alexander FE, Taylor GM, Kelsey AM, Birch JM. An infectious aetiology for childhood brain tumours? Evidence from space-time clustering and seasonality analyses. Br J Cancer. 2002; 86:1070–1077. [PubMed: 11953851]

TABLE I

STUDY POPULATION CHARACTERISTICS BY GLIOMA STATUS

		Glioma Cases (n=489) n(%)	Controls (n=540) n(%)	p-value
Sex				0.06
	Male	270 (55.2)	266 (49.3)	
	Female	219 (44.8)	274 (50.7)	
Family History of Cancer				0.87
	Yes	265 (56.6)	296 (30.0)	
	No	203 (43.4)	222 (42.9)	
Radiation Exposure				0.004
	Yes	22 (4.6)	8 (1.5)	
	No	462 (95.5)	522 (98.5)	
Season of Birth				0.83
	Spring	115 (23.6)	134 (25.1)	
	Summer	143 (29.3)	145 (27.2)	
	Autumn	125 (25.6)	133 (25.0)	
	Winter	105 (21.5)	121 (22.7)	
Age				0.37
	<50 years	251 (51.3)	262 (48.5)	
	≥50 years	238 (48.7)	278 (51.5)	
Highest Level of Education				0.0001
	High School or Less	111 (22.9)	74 (13.7)	
	Some College or Beyond	374 (77.1)	466 (86.3)	
History of Smoking				0.14
	Yes	202 (41.3)	248 (45.9)	
	No	287 (58.7)	292 (54.1)	

TABLE II

FINAL LOGISTIC REGRESSION MODELS DESCRIBING THE EFFECTS OF BIRTH ORDER (A) AND SIBSHIP SIZE (B) ON GLIOMA STATUS

	Logistic regression OR (95% CI)	
	Panel A	**Panel B**
Birth Order	0.87 (0.79–0.97)	
Sibship Size (No. of siblings)		0.97 (0.91–1.04)
Sex		
Female	1.00 (reference)	1.00 (reference)
Male	1.35 (1.04–1.75)	1.35 (1.04–1.75)
Family History of Cancer		
No	1.00 (reference)	1.00 (reference)
Yes	1.04 (0.79–1.36)	1.01 (0.77–1.32)
Highest Level of Education		
Some College or Beyond	1.00 (reference)	1.00 (reference)
High School or Less	2.11 (1.48–3.00)	2.02 (1.42–2.87)
Age in years	0.94 (0.90–0.98)	0.94 (0.90–0.98)
Birth cohort		
1920–1940[1]	1.00 (reference)	1.00 (reference)
1941–1950	0.49 (0.28–0.87)	0.48 (0.27–0.85)
1951–1960	0.28 (0.11–0.70)	0.26 (0.10–0.64)
1961–1970	0.18 (0.05–0.65)	0.16 (0.04–0.59)
1971–1980	0.08 (0.01–0.43)	0.07 (0.01–0.39)
Post-1980	0.08 (0.01–0.70)	0.07 (0.01–0.64)

[1] These two decades are grouped together because of the small number of participants born between 1920 and 1930.