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Early life exposures and the risk of adult glioma

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Abstract Exposure to common infections in early life may stimulate immune development and reduce the risk for developing cancer. Birth order and family size are proxies for the timing of exposure to childhood infections with several studies showing a reduced risk of glioma associated with a higher order of birth (and presumed younger age at infection). The aim of this study was to examine whether birth order, family size, and other early life exposures are associated with the risk of glioma in adults using data collected in a large clinic-based US case-control study including 889 glioma cases and 903 community controls. A structured interviewer-administered questionnaire was used to collect information on family structure, childhood exposures and other potential risk factors. Logistic regression was used to calculate odds ratios (OR) and corresponding 95 % confidence intervals (CI) for the association between early life factors and glioma risk. Persons having any siblings were at significantly lower risk for glioma when compared to those reporting no siblings (OR = 0.64; 95 % CI 0.44–0.93; $p = 0.020$). Compared to first-borns, individuals with older siblings had a significantly lower risk (OR = 0.75; 95 % CI 0.61–0.91; $p = 0.004$). Birth weight, having been breast fed in infancy, and season of birth were not associated with glioma risk. The current findings lend further support to a growing body of evidence that early exposure to childhood infections reduces the risk of glioma onset in children and adults.

Keywords Glioma · Birth order · Siblings · Birth weight · Breast feeding

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Introduction

The etiology of glioma, the most common primary malignant adult brain tumor, is largely unknown. Ionizing radiation [1, 2] and rare hereditary disorders [3] are the only established risk factors for glioma, and these factors only account for a small proportion of cases. There is little evidence for associations with reproductive history [4, 5], smoking [6], alcohol consumption [7], diet [8–10], and occupational history [11, 12]. There is however growing evidence that immunologic factors are associated with risk of glioma onset in adults; a history of allergies or asthma [13] and elevated levels of immunoglobulin E [14, 15] have both been reported to increase risk, as have polymorphisms in genes modulating immune response [16–19].

Furthermore, there is circumstantial evidence that childhood infections may reduce the risk of brain tumor development later in life [20–23].

That exposure to infectious agents in childhood is instrumental in the development of adult brain tumors is supported by several lines of evidence. Exposure to common viruses in childhood may stimulate maturation of the immune system [24], which may in turn reduce tumor incidence in the adult. Birth order [20–22], family size [20–22] and season of birth [23] have been used as proxies for the timing of infection in childhood. Children of higher birth order (i.e., younger siblings) may be exposed to infections at an earlier age by older siblings. In several studies an excess risk of adult glioma [20–22] was demonstrated among first-born children whose first exposure to infection may be delayed until they begin school or are exposed to other children in daycare. Family size is an additional proxy for exposure to infectious agents in early life since individuals in large families have more opportunity to acquire an infection from close contact with many family members. Some [21, 22] though not all [20] studies have suggested altered risk of glioma depending on family size. Season of birth which may coincide with outbreaks of flu offers a further proxy for the timing of first infection, with season of birth observed to influence risk in some though not all studies (reviewed by Efird [23]). Supporting a potential protective role for early infections and glioma risk, one study observed that glioma cases were significantly less likely to report a history of chicken pox [25], and two studies found higher levels of immunoglobulin G antibodies for varicella-zoster virus among controls [25, 26], however, these studies did not consider timing of infection.

The aim of the present study was to examine the association between birth order, family size, and other proxies for early life exposures with the risk of adult-onset glioma in a large US case-control study of 889 glioma cases and 903 controls.

Materials and methods

Study population and data collection

A description of the study has been published previously [27]. Briefly, subjects were enrolled in a clinic-based case-control study examining risk factors for glioma. All individuals in the present analysis were aged 18 or older and had a recent (within 3 months) primary diagnosis of glioma. Glioma cases were identified in neurosurgery and neuro-oncology clinics in the Southeastern US including Vanderbilt University Medical Center (Nashville, TN); Moffitt Cancer Center (Tampa, FL); University of Alabama

at Birmingham (Birmingham, AL); Emory University (Atlanta, GA), and the Kentuckiana Cancer Institute (Louisville, KY). Controls included friends and other non-blood related associates of the cases as well as residents from the same communities as the cases identified in white page listings with frequency matching to cases on state of residence, age and gender. Controls were excluded if they reported a personal history of a brain tumor. Eighty-seven percent of eligible glioma patients were enrolled in the study, a median of 1.0 month following the glioma diagnosis (interquartile range 2 weeks–1.7 months). An estimated 50 % of contacted eligible households yielded a participating control. Study protocols were approved by the institutional review committees at each participating center and all study participants provided written informed consent.

Structured interviewer-administered questionnaires were used to collect data on demographic characteristics and potential glioma risk factors. Relevant to the present analysis, participants were asked to report the total number of older and younger full and half siblings; for half siblings, the biologic parent in common with the subject was also reported. In the present analysis, only siblings born to the same mother (i.e., full siblings and maternal half siblings) were included in the analysis under the assumption that children more often remain with the mother in the event of divorce. Subjects were also asked to report their birth weight and whether they had been breast fed as an infant (yes/no) and approximately 58 and 80 % of subjects, respectively, were able to report these early-life exposures. Among 83 control subjects administered a second, shortened version of the interview, excellent reliability was observed for birth weight ($r^2 = 0.96$) and ever breast fed in infancy (97 % agreement). (Family structure questions were not included in the second interview.)

Statistical analysis

The distribution of demographic characteristics among cases and controls was compared using the Chi-squared test for categorical variables and the Mann–Whitney U test for continuous variables. Birth order was defined as the total number of older full and maternal half siblings plus one. Sibship size (number of siblings) was the total number of full and maternal half siblings. Birth weight was categorized as low (<2,500 g), normal (2,500–3,999 g), or high (≥4,000 g). Season at birth was categorized as fall (September, October, November), winter (December, January, February), spring (March, April, May) or summer (June, July, August).

To examine the association between early life factors and glioma risk, logistic regression models adjusting for age at diagnosis (5-year categories), state of residence, race

(Caucasian/non-Caucasian), gender, and education (high school or less, some college, college graduate, graduate education) were used to calculate odds ratios (ORs) and corresponding 95 % confidence intervals (CIs) for individual exposures. For the birth order analysis, all first-born subjects, including individuals with no siblings, were included in the reference group. To test for linear trend, birth order was included in the model as an ordinal term. All statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

Results

The median age of participants was 54 years for cases (range 18–88) and 56 years for controls (range 18–90). The majority of cases (59 %) and controls (57 %) were male. Compared to controls, glioma cases were slightly younger and less educated (not shown). Of the 889 glioma cases, 546 (61 %) were glioblastomas (GBM), 188 (21 %) were lower grade astrocytomas, 125 (14 %) were oligodendrogliomas, and 30 (3 %) were gliomas of other or unspecified histologic types.

Table 1 shows the relationship of glioma risk with total number of siblings. Compared with having 2 siblings, persons having no siblings had a 65 % increased risk of developing glioma (OR = 1.65; 95 % CI 1.10–2.47). No significant differences were observed in persons with 1 sibling or 3–4 siblings, with a modest and nonsignificant excess risk observed in persons with 5 siblings or greater (OR = 1.30; 95 % CI 0.93–1.81). Having any siblings was associated with a significantly reduced risk of glioma when compared to having no siblings (OR = 0.64; 95 % CI 0.44–0.93).

We next considered associations according to birth order (Table 2). Compared to only children or those born first among their siblings, having any older siblings was associated with a significantly lower risk for glioma development

Table 1 Association between sibship size and glioma

	Controls (N = 903)	Cases (N = 889)	OR (95% CI)[a]
Number of siblings			
None	54	79	**1.65 (1.10–2.47)**
1	255	231	1.03 (0.79–1.34)
2	230	209	1.00 (Ref)
3–4	250	233	1.05 (0.80–1.37)
≥5	114	137	1.30 (0.93–1.81)
Any siblings vs. no siblings			**0.64 (0.44–0.93)**

Bold numbers indicate a *p* value <0.05

[a] Model adjusted for age, gender, race, state of residence and education

(OR = 0.75; 95 % CI 0.61–0.91). The inverse association was consistent for GBM (OR = 0.77; 95 % CI 0.61–0.97), lower grade astrocytomas (OR = 0.66; 95 % CI 0.47–0.92), and oligodendrogliomas (OR = 0.68; 95 % CI 0.45–1.02), though the latter result was imprecise. The protective influence of having older siblings was sustained after excluding subjects with no siblings from the reference group (OR = 0.77; 95 % CI 0.63–0.95 for all gliomas combined). A consistent inverse association was observed in those born second, third and fourth (odds ratios: 0.72, 0.70 and 0.76, respectively, for all gliomas) whereas no protective association was observed in persons born 5th or higher (OR = 0.94; 95 % CI 0.67–1.33) in their families. All results were similar when only full siblings were considered in the analysis and when both maternal and paternal half siblings were included in the determination of birth order (not shown).

The association of birth order in relation to family size is shown in Table 3. A pattern of reduced risk in later-born siblings was observed in families with 2, 3 or 4 children, though associations were significant only in the latter families. In families with 4 children, an approximately 50 % reduction in risk was observed in those born second (OR: 0.56), third (OR: 0.47), or fourth (OR: 0.52) when compared to those born first in the family. In contrast, no association with birth order was observed in larger families (5 or more children).

Finally, we considered whether glioma risk varies according to birth weight, having been breast fed, and season at birth. Glioma risk was similar among individuals reporting a low (OR = 0.96; 95 % CI 0.57–1.63) or high (OR = 1.09; 95 % CI 0.74–1.63) birth weight as compared to those reporting a normal birth weight. Having been breast fed as an infant was also unrelated to glioma risk (OR = 1.12; 95 % CI 0.87–1.43). No differences were observed between cases and controls in season of birth, with odds of glioma similar among those born in winter (OR = 0.96; 95 % CI 0.74–1.24), spring (OR = 0.97; 95 % CI 0.75–1.26), and summer (OR = 1.03; 95 % CI 0.80–1.33) when compared to those born in the fall.

Discussion

To our knowledge this is the largest case-control study to examine family structure and other early life exposures in relation to adult-onset glioma. Having any siblings and, in particular, having any older siblings was associated with a reduced glioma risk. No associations were demonstrated for the other early life factors examined. Our findings add to a growing literature suggesting that a higher birth order and by implication earlier exposure to childhood infections may reduce the risk of glioma occurrence later in life.

The current findings for birth order are generally consistent with previous studies. In a case-control study that

Table 2 Association between birth order and glioma risk by histologic subtype

	Controls (N = 903)	All gliomas		GBM		Lower grade astrocytomas		Oligodendrogliomas	
		Cases (N = 889)	OR (95 % CI)[a]	Cases (N = 546)	OR (95 % CI)[a]	Cases (N = 188)	OR (95 % CI)[a]	Cases (N = 125)	OR (95 % CI)[a]
Birth order[b]									
1	322	371	(ref)	222	(ref)	85	(ref)	55	(ref)
2	299	247	**0.72 (0.57–0.90)**	158	0.77 (0.59–1.01)	47	**0.60 (0.40–0.91)**	32	0.63 (0.38–1.03)
3	135	116	**0.70 (0.52–0.94)**	65	**0.66 (0.46–0.94)**	25	0.64 (0.38–1.07)	21	0.79 (0.44–1.42)
4	66	59	0.76 (0.51–1.13)	33	0.69 (0.43–1.10)	12	0.66 (0.33–1.32)	10	0.87 (0.40–1.90)
≥5	81	96	0.94 (0.67–1.33)	68	0.99 (0.67–1.45)	19	0.95 (0.52–1.76)	7	0.48 (0.20–1.17)
P for trend		0.24		0.30		0.33		0.15	
Not first-born vs. first-born		**0.75 (0.61–0.91)**		**0.77 (0.61–0.97)**		**0.66 (0.47–0.92)**		0.68 (0.45–1.02)	

GBMs encompassed ICD-O code [30] 9440/3; lower grade astrocytic tumors included grade 3 anaplastic astrocytomas (ICD-O 9401/3), grade 1 or 2 astrocytomas (ICD-O 9384/1, 9421/1, 9400/3, 9424/3), and astrocytoma NOS (ICD-O 9400/3); oligodendroglial tumors included mixed oligodendroglial and astrocytic tumors (ICD-O 9382/3) and pure oligodendrogliomas (ICDO 9450/3, 9451/3). Gliomas with rare or unspecified histology were excluded

Bold numbers indicate a p value <0.05

[a] Models adjusted for age, gender, race, state of residence and education

[b] Birth order of 1 includes both subjects with no siblings and first born subjects with younger siblings

Table 3 Association between birth order and glioma risk according to family size

Number of children in the family	Birth Order					Not first-born vs. first-born by family size
	1	2	3	4	≥5	
2	(Ref)	0.80 (0.55–1.16)				0.80 (0.55–1.16)
3	(Ref)	0.71 (0.45–1.13)	0.78 (0.47–1.32)			0.74 (0.49–1.12)
4	(Ref)	0.56 (0.29–1.06)	**0.47 (0.24–0.90)**	0.52 (0.26–1.02)		**0.51 (0.30–0.86)**
≥5	(Ref)	1.03 (0.49–2.16)	1.06 (0.51–2.20)	1.01 (0.48–2.14)	1.13 (0.61–2.09)	1.08 (0.61–1.91)

All models are adjusted for age, gender, race, state of residence and education

Bold numbers indicate a p value <0.05

included 489 glioma cases and 540 controls, Amirian et al [20] reported a significant inverse association with a decreasing glioma risk associated with increasing order of birth. The protective influence of a higher birth order was observed in both smaller (<3 children) and larger (≥3 children) families. Another case-control study conducted by Cicuttini et al. [22] including 416 glioma cases and 420 controls demonstrated a significantly higher risk of glioma among first-born when compared to later born persons in a family. The association remained after excluding persons with no siblings from the referent group. Similar to the current study, the authors found no evidence that increasing birth order conferred a progressive reduction in risk. In a third study by Altieri et al [21] based on the Swedish Family-Cancer Database in which 4,783 adult astrocytomas with family composition data were ascertained, the authors reported a higher incidence of astrocytomas in eldest siblings when compared to only children. The study did not address whether eldest children were at increased risk regardless of total sibship size. A striking pattern in the

study of Altieri et al was that an increasing number of *younger* siblings was associated with an increased risk. We could not confirm this association in the present study (P for trend = 0.82); however, data were sparse in these analyses and results imprecise.

Season of birth represents a potential proxy for the timing of infections. Several previous studies examined season of birth in relation to glioma, with mixed results (reviewed in [23]). In the current study, one of the largest to examine the association, season of birth had no relationship to glioma risk. Furthermore, no associations could be demonstrated with other early life factors examined, including breast feeding in infancy which may be a proxy for transmission of viruses from the mother [28, 29].

To our knowledge, this is the largest case-control study to examine birth characteristics and glioma risk. The large size of the study permitted us to examine the association of birth order according to family size, albeit with limited power, and to examine associations according to glioma histology. Other strengths include pathologic confirmation

of all cases and the rapid ascertainment of cases in the study resulting in high accrual rates and a minimal potential influence of survival bias in the data. One limitation of this study and all previous studies was the lack of information on daycare attendance and birth spacing. Daycare attendance at a young age and earlier contact with other children would be expected to attenuate associations for first-born status (assuming a mechanism related to early infection); however, most subjects in the current study were born in an era before daycare attendance was common in preschool-aged children. Birth spacing would also be informative as it might be expected that a greater number of years between the oldest and next younger child would correspond to a larger excess risk associated with first born status. The lack of an association of birth order in the current study among persons from very large families may be due to chance. However, although only speculation, it is also possible that a large family size predisposes an individual to types or patterns of infections that do not confer the benefit of reduced risk of these tumors. Future studies could test directly the timing of onset and types of infections that are common in childhood for association with glioma; however, error in reporting such exposures would make associations difficult to detect, an avoidable limitation in studies of this type. Finally, the lower than optimal response rate among the controls is a potential limitation; however, the consistency of results with previous studies suggests that the results were not materially influenced by selective participation of controls on family size and birth order.

Taken together, available evidence suggests that increased birth order is associated with a reduced incidence of adult glioma, a pattern which has also been observed in pediatric glioma, and several other neural tumors [21]. As argued by Altieri et al. [21] the number of older siblings is likely related to an increased risk of infections early in childhood, while the number of younger siblings or total sibship size is more likely associated to infections or re-infections occurring later in childhood. The pattern of risk in younger and older siblings as observed in the current and previous studies suggest that the association may be complex and that the number, timing, and frequency of infections may play a role in the etiology of adult glioma and other neural tumors. Although the biologic mechanism is still unknown, the present results should spur research on the potential infectious origin of pediatric and adult glioma.

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