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Assessment of type of allergy and antihistamine use in the development of glioma

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Abstract

Background—Allergies have been associated with decreased risk of glioma, but associations between duration and timing of allergies, and antihistamine use and glioma risk have been less consistent. The objective was to investigate this association by analyzing types, number, years since diagnosis, and age at diagnosis of allergies, and information on antihistamine usage, including type, duration, and frequency of exposure.

Methods—Self-report data on medically-diagnosed allergies and antihistamine use were obtained for 419 glioma cases and 612 hospital-based controls from Duke University and NorthShore University HealthSystem.

Results—High- and low-grade glioma cases were statistically significantly less likely to report any allergy than controls (OR= 0.66, 95% CI: 0.49–0.87 and 0.44, 95% CI: 0.25–0.76, respectively). The number of types of allergies (seasonal, medication, pet, food, and other) was inversely associated with glioma risk in a dose-response manner (p-value for trend <0.05). Age at diagnosis and years since diagnosis of allergies were not associated with glioma risk. Oral antihistamine use was statistically significantly inversely associated with glioma risk, but when stratified by allergy status, remained significant only for those with high-grade glioma and no medically-diagnosed allergy.

Conclusions—All types of allergies appear to be protective with reduced risk for those with more types of allergies. Antihistamine use, other than in relationship with allergy status, may not influence glioma risk.

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Impact—A comprehensive study of allergies and antihistamine use using standardized questions and biological markers will be essential to further delineate the biological mechanism that may be involved in brain tumor development.

Keywords

Allergy; brain tumor; glioma; risk factor

Introduction

Gliomas are the most common subgroup of brain tumor, consisting of a variety of histologic subtypes: glioblastoma (WHO grade IV), astrocytoma (WHO grades I–III), oligodendroglioma (WHO grades II–III), and mixed glioma (WHO grade II–III). The etiology of this tumor subgroup remains elusive, however. Family history of glioma and exposure to high-dose ionizing radiation are the only known risk factors (1–6). Allergies and/or atopic disease, on the other hand, have been associated with a significantly decreased risk of glioma in many (7–16), but not all (17–21), studies. The decreased risk associated with glioma has been hypothesized to be the result of an increase in immune surveillance related to atopic disease; this hyperactive immune surveillance may limit abnormal cell growth (14). However, the specific mechanism through which atopic disease may influence glioma risk has not been identified and non-causal associations with glioma risk have not been ruled out.

Antihistamines, by virtue of their ability to interact with and inhibit the H1-receptor, are used to treat allergy and cold symptoms orally, as well as dermally to treat allergic manifestations of the skin, such as hives or itching due to insect bites, or eyes. In addition, some antihistamines, such as diphenhydramine hydrochloride, have sedative effects and are used as sleep-aids. Antihistamines may interact with allergic conditions to influence glioma risk or may influence glioma risk directly. Similar to the inverse association with allergy, antihistamine use has been inversely associated with glioma risk (9). However in a more recent study, glioma risk in allergy sufferers was increased in those who reported regular antihistamine use, while there was no association between glioma risk and antihistamine use in those who did not have allergies (22). In addition, as diphenhydramine hydrochloride was found to have equivocal evidence of carcinogenicity for F344/N male rats in a 2-year National Toxicology Program (NTP) carcinogenesis bioassay (23) based on marginally increased incidences of uncommon brain neoplasms (astrocytomas or gliomas) and the test chemical's ability to cross the blood-brain barrier and to get distributed in brain tissue, diphenhydramine hydrochloride was analyzed separately to determine its role as a possible neurocarcinogen in the current study.

In the present manuscript, we investigate the association between allergies and glioma risk in detail by analyzing data on types, number, years since diagnosis, and age at diagnosis of allergies. In addition, information on antihistamine usage, including type, duration, and frequency of exposure, and their potential influence on glioma risk were evaluated.

Methods

Study subjects were recruited during the period February 2006 – April 2008 from Duke University Medical Center (DUMC) in North Carolina and NorthShore University HealthSystem (NSUHS; formerly Evanston Northwestern Healthcare) in Illinois. Survey data were stored and analyzed at University of Illinois at Chicago. A more detailed description of the study population and study design can be found in Rankin et al. (24) and

Il'yasova et al. (15). Institutional Review Board approvals were obtained from all three institutions.

Cases

During the period February 2006 – April 2008, subjects with a histologically confirmed diagnosis (ICDO-3 sites C70.0–C72.9 and C75.1–C75.3) of a primary glioma [glioblastoma (ICDO-3 histology codes 9440–9442), astrocytoma (9400–9411 and 9420–9421), mixed glioma (9382) or oligodendroglioma (9450–9460)], who were 18 or older, English speaking, and residents of the United States were eligible for participation in the study. Among those who consented, 419 cases (51% of eligible) completed the self-report surveys by the end of the study (January 2010). High-grade glioma was defined as WHO grade III or IV tumors, including glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic mixed glioma, etc. Low-grade glioma was defined by WHO grade I or II, including astrocytoma, NOS, fibrillary astrocytoma, oligodendroglioma, mixed glioma, etc. One case was unable to be classified by grade and was excluded from the analysis.

Controls

Hospital-based controls were selected from the patients seen at a DUMC orthopedic or NSUHS neurology clinic and were recruited in the clinic at the time of their doctor's appointment. A detailed description of recruitment procedures has been previously published (15). Controls were frequency-matched to cases by age (10-year interval), gender, and race/ethnicity and were considered eligible if they were aged 18–80 years, resided within the United States, had no history of brain tumors or any cancers, had no history of neurodegenerative disease (amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease, Alzheimer's disease, Parkinson's disease, vascular dementia, dementia with Lewy bodies, frontotemporal dementia, Huntington's disease, or Niemann-Pick disease), and were fluent in English. Among those who consented, 612 controls (71%) completed the self-report surveys by the end of the study (January 2010).

Data Collection

Subjects who consented to participate completed either a web-based or telephone survey that focused on occupational and environmental exposures associated with known or suspected animal neurocarcinogens, as well as demographics, family history, and medical history. For the allergy and asthma questions, participants were asked to indicate whether any healthcare worker had ever told them before two years ago that they had the condition and, if so, the age at which they were diagnosed. Further detail regarding information on allergies included asking the participant to indicate the number of individual allergies (0, 1, 2, 3+) within each of the following types/groups of allergy: seasonal (pollens, molds, etc.), pets, medications, foods (wheat, peanuts, soy, tree nuts, eggs, milk, fish/ shellfish, other) and other allergies. For example, a person allergic to cats, dogs, ragweed, and aspirin would have reported 2 pet allergies, 1 seasonal allergy, 1 medication allergy, and no food or other allergies. The overall number of types of allergies was calculated by summing whether a person positively reported any medically-diagnosed allergies to seasonal triggers, pets, medications, foods, or other allegens for a maximum potential score of 5. For the example given above, the number of types of allergies would be 3 (pets, seasonal, and medications). Years since diagnosis of allergies were estimated by calculating the difference between the age at brain tumor diagnosis or interview and the age at allergy diagnosis. In addition, participants were asked about medications they may have used on a “regular basis for at least one month” before two years ago. Detailed information on antihistamine use was collected through a number of questions which probed for specific details on the specific brands of prescription and over-the-counter antihistamines used for allergies, colds/flu, sleeping aids, anti-itch remedies, and eye drops. In both cases, oral and dermal antihistamine applications were ascertained.

Participants were also asked about frequency (never, rarely, sometimes, often) and duration (<10 years or ≥ 10 years) for each brand that was used. As diphenhydramine hydrochloride was a possible neurocarcinogen of interest, a medication grouping consisting of any antihistamine, cold/flu remedy, sleep aid, eye drop, or anti-itch cream that contained this compound was analyzed separately.

Statistical Analysis

Characteristics of cases with high grade and low grade gliomas were compared with those of hospital controls using chi-square tests. The association between each exposure and glioma risk, adjusted for age, race, gender, education, and clinic site, was estimated from logistic regression models comparing all cases to hospital controls, as well as cases with high-grade and low-grade tumors (where sample size allowed) to hospital controls. Exposure variables for overall allergies, individual allergies, number of allergies, age at allergy onset, years since allergy diagnosis, and antihistamine use were examined in several ways: as dichotomous variables for any versus no exposure, as dummy variables for each level of exposure (i.e. number of allergies, number of types of allergies) versus a common referent group of no exposure, and as ordinal variables to test for a dose-response relationship. Adjusted odds ratios (adjOR) and 95% Confidence Intervals (95% CI) were estimated for the dichotomous and dummy variables and p-values were reported for ordinal versions of the variables when the odds ratios for increasing exposure demonstrated a possible trend (alpha=0.05). Models for antihistamine use were then run separately for those with and without a history of allergies and/or asthma and stratum-specific adjORs and 95% CIs were estimated. SAS Version 9.2 (SAS Institute: Cary, NC) was used for all analyses.

Results

Data from 419 (344 high-grade and 75 low-grade) glioma cases and 612 hospital-based controls were included in the analyses. Demographic characteristics for study subjects are presented in Table 1. Compared to those with high-grade glioma, hospital-based controls were significantly more likely to be older, have a high school or lower education, and report a lower annual income, and were less likely to be male or currently married. Compared to low-grade gliomas, hospital-based controls were significantly older, and less likely to be never married or divorced. In addition, a larger proportion of low-grade gliomas came from NSUHS than Duke compared to high-grade gliomas and controls.

All glioma cases combined, as well as both high-grade and low-grade glioma cases, were significantly less likely to report an allergy diagnosed by medical personnel than hospital-based controls (Odds Ratio (OR) = 0.60, 95% CI: 0.46–0.79; 0.66, 95% CI: 0.49–0.87 and 0.44, 95% CI: 0.25–0.76, respectively; Tables 2 and 3). Glioma risk was inversely associated with having any compared to having none of the following allergy types: seasonal allergies, medication allergies, pet allergies, food allergies (only fish/shellfish allergies were individually statistically significantly inversely associated with glioma risk; data not shown), and other allergies. This association did not reach statistical significance for medication allergies in those with high-grade or low-grade glioma or for pet or food allergies in those with high-grade glioma only. The number of different allergies of that type was also inversely associated with glioma risk, such that as the number of that allergy type increased, glioma risk decreased (Table 2). For example, in the comparison with all glioma cases, the adjusted odds ratio for those who reported 1 seasonal allergy was 0.84 compared to those with no seasonal allergies, while similar adjusted ORs for those reporting 2, or 3 or more different seasonal allergies was 0.72 and 0.36, resulting in a statistically significant inverse trend (Table 2).

Across the five types of allergies (seasonal, medication, pet, food, and other), the number of different types of allergies was inversely associated with glioma risk in a statistically significant dose-response manner for all glioma cases combined and for both high-grade and low-grade gliomas (Tables 2 and 3). Among those reporting any medically-diagnosed allergy, age at diagnosis was not significantly associated with risk of all glioma cases combined or high-grade or low-grade glioma. In addition, among those with any allergies, there were no significant differences in risk of all glioma or high-grade glioma in those who were diagnosed with allergy less than 10 years prior to brain tumor diagnosis or interview compared to those diagnosed 10 or more years prior (Table 2).

Oral antihistamine use was also inversely associated with glioma risk, although the adjusted OR was not statistically significant for those with low-grade glioma (Table 4). The risk was similar whether the oral antihistamine was used sometimes/often for less than 10 years or sometimes/often for more than 10 years when compared to those who never used antihistamines. Results were almost identical when both oral and dermal antihistamine use was evaluated (data not shown). For subjects who reported a history of medically-diagnosed allergy, a non-significant inverse association between oral antihistamine use and risk of all cases combined, high- and low-grade glioma were observed (data not shown). No associations were observed in any subgroup for those who reported no medically-diagnosed allergies.

When restricted to use of any oral medication containing diphenhydramine hydrochloride, a significant inverse association was found for all cases combined and for those with high-grade glioma (OR = 0.73, 95% CI: 0.56–0.95; and 0.66, 95% CI: 0.50–0.87, respectively; Table 4). However, the risk of low-grade glioma was reversed, although not significantly (1.31, 95% CI: 0.77–2.21). Once again, results were very similar when both oral and dermal usage of medications containing diphenhydramine hydrochloride was evaluated (data not shown). When stratified by history of medically-diagnosed allergy, a significant association was only found between oral diphenhydramine hydrochloride use and risk of high-grade glioma for those with no medically-diagnosed allergy (OR = 0.66, 95% CI: 0.46–0.95), while those with medically-diagnosed allergy had a non-significantly reduced risk (OR= 0.76, 95% CI: 0.49–1.19; data not shown).

Discussion

An inverse association between history of allergies and risk of glioma, as found in this study, is one of the most consistent associations in the brain tumor literature. Although not all statistically significant associations, a decreased risk of glioma has been observed in those with allergic disease (including allergies, asthma, and/or eczema) in many studies (7–13,15–19), but not all (20–21). A meta-analysis of several of these studies found a pooled relative risk of glioma of 0.61 (95% CI: 0.55–0.67) associated with allergy (14). The authors concluded that this strong inverse relationship was unlikely to be explained away by bias due to proxy responses or publication bias.

Differences in the definition of allergy may influence comparisons of results between studies. Allergies may be grouped with other atopic diseases (such as asthma and/or eczema) or each atopic disease may be investigated individually. For example, Wigertz et al. (13) found an odds ratio of 0.70 (95% CI: 0.61–0.80) for glioma associated with a diagnosis of any of the following atopic conditions: asthma, hay fever, eczema, or other type of allergy; however, results were similar and statistically significant for each allergic condition individually (asthma, eczema, hay fever, and food allergy). Similarly, Wiemels et al. (11) found that pollen, dairy and nut allergies were significantly less common in cases than controls, while most other allergens had odds ratios of less than one. Alternatively, allergies

may be defined narrowly; for example, only including those with seasonal allergies. In fact, a cohort study and a case-control study found no association with glioma risk and history of hay fever specifically (20–21). In our study, we asked study subjects to report only allergies that had been diagnosed by a doctor or other medical personnel. Studies which also allowed reporting of self-diagnosed allergies would have a higher frequency of allergies than our study, which may also influence their results and overall consistency.

The present study found a significant trend in risk reduction of glioma by number of allergy types (seasonal, medication, pet, food, and/or other), as well as by actual number of allergies for each allergy type, consistent with the results of Wiemels et al. (11) who also found a significant dose-response with increasing numbers of allergens. Similar to findings of previous studies, the present study also found no statistically significant trend in glioma risk with duration of the allergic condition (9,21) or age at first allergy diagnosis (9,12). However, one previous study found greater risk reduction in those with a recent diagnosis of asthma and hay fever (12), while a second study found that reduced risks of glioma were confined to current rather than past atopic conditions of eczema, hay fever, and allergy overall, but not asthma (13).

Antihistamine use has been investigated in several studies. Similar to the results of our study, both Schlehofer et al. (9) and Schoemaker et al. (12) found an inverse association with glioma risk and antihistamine use, although the later study was specific to those with hay fever. Alternatively, Scheurer et al. (22) found that antihistamine use among those reporting a history of asthma or allergies was associated with an increased risk of glioma (OR= 2.54; 95% CI: 1.28, 5.03), especially for those who reported ≥10 years of regular antihistamine use. There was no association with glioma risk and antihistamine use among those reporting no history of asthma or allergies (OR=0.82; 95% CI: 0.47, 1.44). Our study did not confirm a specific aspect of the Scheurer study, namely the analysis of overall antihistamine use or use of diphenhydramine hydrochloride-containing products by duration of use or stratified by history of allergy. However, differences in study design and characteristics (such as the way questions were asked) prevent a direct comparison of results. For example, because the Scheurer study included all individuals with medically diagnosed allergies or asthma, individuals diagnosed with asthma but not allergies were included in their estimates. The current study restricts analysis to those with medically diagnosed allergies, which may have resulted in a more homogenous group of subjects and may account for some of the discrepancies between studies.

While there is a paucity of literature on the carcinogenicity of diphenhydramine hydrochloride, a study (23) by the National Toxicology Program reported equivocal evidence for a marginally increased incidence of gliomas in male (but not female) F344/N rats receiving high (i.e., 625 ppm), but non-toxic, doses of diphenhydramine hydrochloride over a 2-year period compared to controls. The same study found no evidence of carcinogenic activity induced by exposure to diets containing up to 313 ppm diphenhydramine hydrochloride in $B6C3F_1$ mice (23). The role of diphenhydramine hydrochloride as a possible neurocarcinogen in humans remains undetermined and warrants further study.

Limitations of the study include the potential for both recall and selection bias. There were no proxy interviews conducted for this study; however, study subjects were allowed to have assistance when completing the survey. The accuracy of recalled details related to their allergy diagnosis or medication usage may be different between cases and controls. Cases with brain tumors may have partial cognitive impairment which may affect their ability to accurately recall details, but cases may also spend more time contemplating potential causes of their illness compared to controls. Despite potential differences in the recall of details,

reporting of medically diagnosed allergies (as was done in this study) is likely to be accurate, similar to what was found for asthma (25). Case subjects who completed the survey were more likely to be younger and were more likely to be recruited by Duke University, but did not differ by gender or race, compared to subjects who did not consent or who consented but did not complete the survey. It is possible that these differences may have resulted in bias. In addition, small numbers of subjects, especially for those with low-grade glioma, may limit the interpretations that can be made from this data, as negative results may be because the study was underpowered, while positive results may be due to chance alone. Although controls were selected from clinics at the respective institutions, the conditions for which the controls were being treated at the time are not known to be associated with allergic conditions. In addition, although we made an attempt to frequency-match, the distributions of control characteristics were significantly different from cases. Results were adjusted for age, race, gender, education, and study site, but there is the potential that other factors not controlled for in the analyses could influence the results. Finally, as the biological mechanism is still unknown, we cannot rule out the possibility that the primary effect is due to environmental or other factors related to allergies that are unmeasured in this study, with the factors measured here being mediators.

In summary, our results confirm the overall association with allergies and the trend of decreased glioma risk with increasing number of allergies. The lack of an association with duration and age at onset of allergies and antihistamine usage was consistent with some but not all previous studies. Separate analysis of the antihistamine, diphenhydramine hydrochloride, did not reveal any increased risk associated with gliomas. A comprehensive study of all aspects of allergies and atopic disease, as well as antihistamine use, in those with and without brain tumors using standardized questions and biological markers will be essential to further delineate the biological mechanism that may be involved in brain tumor development.

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Table 1

Descriptive characteristics of glioma cases and hospital-based controls

		All Cases (n=419)	Cases with High Grade Tumors (n=344)	Cases with Low Grade Tumors (n=75)	Hospital-Based Controls (n=612)
Gender*	Male	248 (59.2)	217 (63.1)	31 (41.3)	280 (45.7)
	Female	171 (40.8)	127 (36.9)	44 (58.7)	332 (54.3)
Age*†	<20	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.7)
	20–29	43 (10.3)	28 (8.1)	15 (20.0)	38 (6.2)
	30–39	48 (11.5)	30 (8.7)	18 (24.0)	56 (9.2)
	40–49	91 (21.7)	74 (21.5)	17 (22.7)	98 (16.0)
	50–59	116 (27.7)	99 (28.8)	17 (22.7)	160 (26.3)
	60–69	99 (23.6)	93 (27.0)	6 (8.0)	161 (26.3)
	70–79	21 (5.0)	19 (5.5)	2 (2.7)	69 (11.3)
	80+	1 (0.2)	1 (0.3)	0 (0.0)	26 (4.3)
Race/Ethnicity	White, NH	383 (91.4)	315 (91.6)	68 (90.7)	526 (86.0)
	Black, NH	14 (3.3)	13 (3.8)	1 (1.3)	49 (8.0)
	Hispanic	8 (1.9)	6 (1.7)	2 (2.7)	14 (2.3)
	Other	14 (3.3)	10 (2.9)	4 (5.3)	23 (3.8)
Marital status*†	Married	326 (77.8)	280 (81.4)	46 (61.3)	427 (69.8)
	Divorced	30 (7.2)	18 (5.2)	12 (16.0)	65 (10.6)
	Separated	3 (0.7)	3 (0.9)	0 (0.0)	14 (2.3)
	Widowed	7 (1.7)	6 (1.7)	1 (1.3)	42 (6.9)
	Never Married	53 (12.6)	37 (10.8)	16 (21.3)	64 (10.5)
Education*	0–8 yrs	2 (0.5)	2 (0.6)	0 (0.0)	10 (1.6)
	9–12	102 (24.3)	80 (23.3)	22 (29.3)	181 (29.6)
	13–16	183 (43.7)	146 (42.4)	37 (49.3)	266 (43.5)
	>16	132 (31.5)	116 (33.7)	16 (21.3)	155 (25.3)
Income*‡	<$50,000	108 (26.4)	79 (23.6)	29 (39.2)	226 (37.7)
	$50–99,999	139 (34.0)	117 (34.9)	22 (29.7)	220 (36.7)
	$100,000–150,000	91 (22.3)	80 (23.9)	11 (14.9)	99 (16.5)

		All Cases (n=419)	Cases with High Grade Tumors (n=344)	Cases with Low Grade Tumors (n=75)	Hospital-Based Controls (n=612)
	>$150,000	71 (17.4)	59 (17.6)	12 (16.2)	54 (9.0)
Site†	NSUHS	71 (17.0)	48 (14.0)	23 (30.7)	71 (11.6)
	Duke	348 (83.0)	296 (86.0)	52 (69.3)	541 (88.4)

*p-value for Chi-square test comparing high grade to hospital controls is <0.05

†p-value for Chi-square test comparing low grade to hospital controls is <0.05

‡Income was missing for 9 cases with high grade tumors 1case with a low grade tumor and 13 controls

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Table 2

Associations between allergy, allergy type, number of allergies, age at onset and years since diagnosis of allergies and risk of glioma

Allergies	All cases (n=420)‡	Cases with High Grade Tumors (n=344)‡	Hospital-Based Controls (n=612)‡	adjOR† 95% CI) All Cases vs Controls	adjOR† (95% CI) High Grade vs Controls
Any Allergy	140 (33.3)	120 (34.9)	282 (46.1)	0.60 (0.46, 0.79)	0.66 (0.49, 0.87)
Seasonal Allergy					
Any vs None	111 (26.6)	95 (27.9)	243 (39.8)	0.55 (0.42, 0.73)	0.59 (0.44, 0.80)
Number					
0	306 (73.4)	246 (72.1)	367 (60.2)	Ref	Ref
1	40 (9.6)	34 (10.0)	57 (9.3)	0.84 (0.53, 1.31)	0.89 (0.56, 1.42)
2	31 (7.4)	29 (8.5)	53 (8.7)	0.72 (0.45, 1.17)	0.83 (0.51, 1.37)
3+	40 (9.6)	32 (9.4)	133 (21.8)	0.36 (0.24, 0.54)*	0.37 (0.24, 0.57)
Medication Allergy					
Any vs None	74 (17.7)	64 (18.7)	162 (26.6)	0.68 (0.49, 0.93)	0.73 (0.52, 1.02)
Number					
0	344 (82.3)	278 (81.3)	447 (73.4)	Ref	Ref
1	46 (11.0)	40 (11.7)	82 (13.4)	0.77 (0.52, 1.15)	0.82 (0.54, 1.25)
2	13 (3.1)	11 (3.2)	28 (4.6)	0.70 (0.35, 1.39)	0.74 (0.35, 1.53)
3+	15 (3.6)	13 (3.8)	52 (8.5)	0.49 (0.26, 0.90)	0.54 (0.28, 1.03)*
Pet Allergy					
Any vs None	51 (12.3)	43 (12.7)	107 (17.6)	0.60 (0.41, 0.88)	0.68 (0.46, 1.01)
Number					
0	365 (87.7)	297 (87.4)	501 (82.4)	Ref	Ref
1	25 (6.0)	22 (6.5)	53 (8.7)	0.65 (0.39, 1.09)	0.76 (0.45, 1.30)
2	14 (3.4)	12 (3.5)	15 (2.5)	1.12 (0.52, 2.41)	1.21 (0.54, 2.68)
3+	12 (2.9)	9 (2.7)	39 (6.4)	0.34 (0.17, 0.68)	0.36 (0.17, 0.78)
Any Food Allergy					
Any vs None	24 (5.8)	22 (6.5)	61 (10.0)	0.58 (0.35, 0.97)	0.69 (0.41, 1.16)
Number					

Allergies	All cases (n=420)‡	Cases with High Grade Tumors (n=344)‡	Hospital-Based Controls (n=612)‡	adjOR† 95% CI) All Cases vs Controls	adjOR† (95% CI) High Grade vs Controls
0	392 (94.0)	318 (93.3)	548 (89.8)	Ref	Ref
1	19 (4.6)	17 (5.0)	34 (5.6)	0.85 (0.47, 1.56)	1.00 (0.54, 1.86)
2+	6 (1.4)	6 (1.8)	28 (4.6)	0.30 (0.12, 0.74)*	0.38 (0.15, 0.96)
Other Allergy					
Any vs None	27 (6.5)	21 (6.2)	105 (17.3)	0.34 (0.22, 0.54)	0.33 (0.20, 0.55)
Number					
0	389 (93.5)	319 (93.8)	501 (82.7)	Ref	Ref
1	20 (4.8)	16 (4.7)	60 (9.9)	0.44 (0.26, 0.75)	0.43 (0.24, 0.78)
2+	7 (1.7)	6 (1.5)	45 (7.4)	0.22 (0.10, 0.49)*	0.19 (0.07, 0.49)*
Number of Types of Allergies					
0	280 (67.6)	224 (66.3)	330 (54.8)	Ref	Ref
1	46 (11.1)	40 (11.8)	62 (10.3)	0.89 (0.58, 1.37)	0.95 (0.61, 1.49)
2	50 (12.1)	40 (11.8)	95 (15.8)	0.61 (0.41, 0.90)	0.61 (0.40, 0.93)
3	23 (5.6)	22 (6.5)	65 (10.8)	0.45 (0.27, 0.76)	0.55 (0.33, 0.94)
4+	15 (3.6)	13 (3.6)	50 (8.3)	0.36 (0.19, 0.67)*	0.39 (0.20, 0.75)*
Ages at diagnosis of any allergy (among those with allergies)	All Cases with Allergies (n=138)	Cases with High Grade Tumors and Allergies (n=118)§	Hospital-Based Controls and Allergies (n=271)§	adjOR† (95% CI) All Cases vs Controls	adjOR† (95% CI) High Grade vs Controls
<20	64 (46.4)	53 (44.9)	111 (41.0)	Ref	Ref
20–39	48 (34.8)	42 (35.6)	90 (33.2)	1.19 (0.72, 1.96)	1.20 (0.71, 2.03)
40–79	26 (18.8)	23 (19.5)	70 (25.8)	1.05 (0.56, 1.95)	1.02 (0.53, 1.97)
Years since diagnosis of any allergy (Among those with allergies)					
<10 years	21 (15.6)	19 (16.2)	38 (13.5)	1.24 (0.68, 2.25)	1.38 (0.74,2.57)
10+years	114 (84.4)	98 (83.8)	243 (86.5)	Ref	Ref

† Adjusted for age, gender, race, education, and study site

‡ Information about allergy types was missing for 3 cases with high grade glioma and 2 hospital controls, so the sample sizes for all allergy type analyses are 341 and 610 in these groups, respectively

§ Age at diagnosis of allergies and years since diagnosis of allergies is missing for 2 cases with high grade gliomas and 11 hospital controls with allergies, resulting in the sample sizes listed here

* p-value for trend was <0.05

Table 3

Associations between allergy, allergy type, number of types of allergies and age at onset of allergies and risk of low grade glioma

Allergies	Cases with Low Grade Tumors (n=75)	Hospital-Based Controls (n=612)‡	adjOR† (95% CI) Low Grade vs Controls
Any Allergy	20 (26.7)	282 (46.1)	0.44 (0.25, 0.76)
Seasonal Allergy	16 (21.3)	243 (39.8)	0.40 (0.22, 0.73)
Medication Allergy	10 (13.3)	162 (26.6)	0.49 (0.24, 1.00)
Pet Allergy	8 (10.7)	107 (17.6)	0.39 (0.18, 0.87)
Any Food Allergy	2 (2.7)	61 (10.0)	0.21 (0.05, 0.91)
Other Allergy	6 (8.0)	105 (17.3)	0.39 (0.16, 0.95)
Number of Types of Allergies			
0	55 (73.3)	330 (54.8)	Ref
1	6 (8.0)	62 (10.3)	0.62 (0.25, 1.57)
2+	14 (18.7)	210 (34.9)	0.39 (0.20, 0.73)*

Ages at diagnosis of any allergy (among those with allergies)	Cases with Low Grade Tumors and Allergies (n=20)	Hospital-Based Controls and Allergies (n=271)§	adjOR† (95% CI) Low Grade vs Controls
<20	11 (55.0)	111 (41.0)	Ref
20+	9 (45.0)	160 (59.0)	0.69 (0.14, 3.34)

† Adjusted for age, gender, race, education, and study site

‡ Information about allergy types was missing 2 hospital controls, so the sample sizes for all allergy type analyses is 610for controls

§ Age at diagnosis of allergies and years since diagnosis of allergies is missing for 11 hospital controls with allergies, resulting in the sample sizes listed here

* p-value for trend was <0.05

Table 4

Overall and duration/frequency of exposure to oral medications and glioma risk

	Cases with High Grade Tumors (n=344)‡	Cases with Low Grade Tumors (n=75)	Hospital-Based Controls (n=612)‡	adjOR† 95% CI) All Cases vs Controls	adjOR† (95% CI) High Grade vs Controls	adjOR† (95% CI) Low Grade vs Controls
Any Oral Antihistamine						
Any (#/%) vs None	166 (48.3)	42 (56.0)	339 (55.4)	0.76 (0.59, 0.99)	0.75 (0.57, 0.99)	0.78 (0.46, 1.33)
Duration/Frequency						
Never	178 (51.9)	33 (44.0)	273 (44.8)	Ref	Ref	Ref
Rarely	79 (23.0)	20 (26.7)	88 (14.5)	1.36 (0.95, 1.92)	1.30 (0.90, 1.89)	1.55 (0.66, 2.50)
Sometimes/Often for <10 yrs	62 (18.1)	18 (24.0)	196 (32.2)	0.52 (0.37, 0.72)	0.50 (0.35, 0.71)	0.55 (0.29, 1.05)
Sometimes/Often for 10+ yrs	24 (7.0)	4 (5.3)	52 (8.5)	0.64 (0.38, 1.06)	0.67 (0.39, 1.14)	0.44 (0.14, 1.40)
Any Oral Medication w/ Diphenhydramine Hydrochloride						
Any (#/%) vs None	147 (42.7)	46 (61.3)	320 (52.3)	0.73 (0.56, 0.95)	0.66 (0.50, 0.87)	1.31 (0.77, 2.21)
Duration/Frequency						
Never	197 (57.3)	29 (38.7)	292 (47.9)	Ref	Ref	Ref
Rarely	84 (24.4)	25 (33.3)	127 (20.8)	0.99 (0.72, 1.36)	0.91 (0.64, 1.28)	1.74 (0.94, 3.22)
Sometimes/Often for <10 yrs	47 (13.7)	17 (22.7)	148 (24.3)	0.56 (0.39, 0.80)	0.48 (0.33, 0.71)	1.06 (0.37, 1.59)
Sometimes/Often for 10+ yrs	16 (4.7)	4 (5.3)	43 (7.1)	0.56 (0.31, 0.99)	0.53 (0.29, 0.99)	0.80 (0.25, 2.56)

† Adjusted for age, gender, race, education, and study site

‡ Duration/frequency of antihistamines was missing for one case with a high grade glioma and three controls; Duration/frequency of diphenhydramine hydrochloride use was missing for two controls