Short Communication

Long-term Anti-inflammatory and Antihistamine Medication Use and Adult Glioma Risk

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Abstract

A personal history of asthma or allergy has been associated with a reduced risk for adult malignant gliomas. Recent reports on the use of nonsteroidal anti-inflammatory drugs (NSAID) and the presence of risk alleles in asthma susceptibility genes showed similar inverse associations. To further explore the relationship between immune mediators and gliomas, we examined the use of NSAID and antihistamines, history of asthma or allergy, and infection in 325 glioma cases and 600 frequency-matched controls from the metropolitan area of Houston, TX (2001-2006). The regular use of NSAID was associated with a 33% reduction in the risk for glioma, suggestive of possible antitumor activity. Surprisingly, regular long-term antihistamine use among those reporting a history of asthma or allergies was significantly associated with a 3.5-fold increase in the risk for glioma. Similar to previous reports, cases in our study were less likely to have reported asthma, allergy, or a history of a number of viral infections (chickenpox or shingles, oral herpes, and mononucleosis) than controls. We therefore speculate that the observed positive association with antihistamine use may reflect an alteration of protective immune factors in susceptible individuals. Our results lend additional support for an important but unknown link between malignant brain tumors and immune mediators. (Cancer Epidemiol Biomarkers Prev 2008;17(5):1277–81)

Introduction

Malignant gliomas are the most common primary brain tumor in adults, yet little is known about their etiology. Epidemiologic studies suggest a lower risk for gliomas among people reporting a history of allergies and asthma (1-10). Schwartzbaum et al. (11) reported that asthma susceptibility gene polymorphisms in *IL4RA* and *IL13* were associated with a decreased risk for adult gliomas; however, they were unable to show significance in a larger analysis (12). Another report suggested a reduced risk for glioma with the use of nonsteroidal anti-inflammatory drugs (NSAID; ref. 13). These studies lend support for a yet unexplained association between immune factors and glioma risk.

Antihistamines, a class of commonly used allergy drugs, have not been well examined in relation to adult gliomas. Studies on the effects of antihistamine use on the risk for pediatric brain tumors largely pursue a direct carcinogenic action of antihistamines as nitrosatable exposures in the brain; however, results have been inconclusive (14-17). A 2-year feeding study (National Toxicology Program, CAS No. 147-24-0, NTP Study TER82067) reported increased incidences of gliomas in male Fischer 344/N rats after administration of diphenhydramine hydrochloride, the most common antihistamine. These drugs act to alleviate symptoms associated with histamine release after exposure to allergens. We speculated that antihistamine use would be more common among persons prone to allergy and more likely to be associated with a decrease in risk, as has been report in previous studies (6, 7, 10). We used data from a case-control study on adult glioma in greater Houston, TX, to examine the relationships between these medications and glioma risk.

Materials and Methods

Subjects. Cases (≥18 years) were newly diagnosed between January 2001 and January 2006 with a glioma (International Classification of Diseases for Oncology, 3rd Edition, codes 9380-9481) and resided in the following Texas counties: Austin, Brazoria, Chambers, Colorado, Fort Bend, Galveston, Harris, Jefferson, Liberty, Montgomery, Orange, San Jacinto, Walker, Waller, and Wharton. Cases were interviewed before radiotherapy or chemotherapy but typically after surgery. Proxies were interviewed for subjects unable to participate because of disability or death. For all cases, diagnosis was confirmed by a neuropathologist at the M. D. Anderson Cancer Center. Controls, frequency-matched

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Table 1. Demographic and inflammation-related characteristics of study subjects, Harris County Adult Glioma Study, 2001-2006

	Controls (n = 600)	Cases (n = 325)	P value*
Age (y) †			
Mean (SE)	50.1 (0.54)	50.6 (0.74)	0.53
Gender † [n (%)]			
Male	311 (52)	188 (58)	0.08
Female	289 (48)	137 (42)	
Race † [n (%)]			
White	476 (79)	264 (81)	0.80
African-American	41 (7)	17 (5)	
Hispanic	71 (12)	37 (11)	
Other	12 (2)	7 (2)	
Education [n (%)]			
<High school	21 (4)	16 (5)	0.001
High school/some college	250 (42)	173 (54)	
College degree	170 (28)	75 (23)	
Advanced degree	159 (26)	57 (18)	
Ever cigarette use [n (%)]	453 (76)	235 (73)	0.32
Ever alcohol use [n (%)]	546 (91)	249 (77)	<0.001
Family history of cancer [n (%)]	468 (78)	261 (80)	0.412
Family history of brain tumor [n (%)]	48 (8)	51 (16)	<0.001
Inflammation-related events			
History of asthma or allergy [n (%)]	202 (34)	44 (14)	<0.001
History of chickenpox [n (%)]	515 (86)	239 (74)	0.001
History of shingles [n (%)]	51 (9)	17 (5)	0.069
History of oral herpes [n (%)]	76 (13)	10 (3)	<0.001
History of mononucleosis [n (%)]	65 (11)	13 (4)	0.001
History of migraine headaches [n (%)]	50 (8)	4 (1)	<0.001
Previous head injury [n (%)]	184 (31)	115 (36)	0.104
Previous stroke [n (%)]	18 (3)	6 (2)	0.292

*P values derived from χ^2 tests for categorical variables and t tests for continuous variables; comparison of cases to controls.
† Matching variables.

to cases by age, gender, and ethnicity, were English-speaking residents of the same Texas counties, obtained through standard random-digit dialing (18, 19). Interested eligible controls were contacted by study personnel to obtain consent and arrange an interview. Overall response rates were 77% for cases and 53% for controls.

Interviews. Structured in-person or telephone interviews using questionnaires and show cards were conducted with consenting cases (or proxies) and controls. Neither cases nor controls were told of the study hypotheses during the interview. In-person interviews were conducted for 46% of cases and 5% of controls; telephone interviews were conducted for 54% of cases and 95% of controls. Subjects answered questions about demographic characteristics, personal and family medical history, and occupational and environmental exposures. The inflammation-related questions of interest consisted of all infectious diseases, self-report of asthma or any allergy, and conditions associated with inflammation in the brain (stroke, migraine headaches, and brain injury). Information on all medications taken during the previous 10 years was also obtained. The two medications of interest for the analysis were anti-inflammatory agents (NSAID) linked with reduced risk for other cancers and antihistamines taken for allergies, which have been shown to confer a reduced risk for gliomas. Subjects were shown or read aloud a list of these drugs (generic and brand names). Response rates to the medication questions among cases and controls did not differ significantly for in-person or telephone interviews. Cases reported similar use for in-person (15% antihistamines, 21% NSAID) and telephone (13% antihistamines, 23% NSAID) interviews. Controls reported slightly higher use for in-person (20% antihistamines, 44% NSAID) compared with telephone (15% antihistamines, 31% NSAID) interviews; however, this was most evident for NSAID use. Participants were asked whether they had taken these drugs on a regular basis for 6 months or more before diagnosis (cases) or time of interview (controls). If the respondent reported regular use, the interviewer asked the specific name of the drug(s) and the duration of regular use; dosage was not obtained.

Data Analysis. Unconditional logistic regression was used to estimate odds ratios and 95% confidence intervals (95% CI). Variables that were significantly related to case status in univariate analysis were evaluated for inclusion in the final logistic model, which was adjusted for age, gender, and race. Reference categories were those who reported no regular medication use. Proxy-reported data did not appreciably alter our findings and were not excluded from our analysis. To be considered a confounder, the characteristics in Table 1 had to be associated with the outcome in the unexposed, associated with the exposure among the controls, and must have changed the point estimate by more than 10% after adjustment. None of the variables were found to be confounders by this method. All analyses were done using Stata version 8.2. All P values are two-sided with a 0.05 level of significance.

Results

We obtained complete interviews from 325 cases, including 33 (4%) proxy reports, and 600 controls.

Table 2. Adjusted odds ratios for the use of antihistamines and anti-inflammatory agents among glioma cases and controls, Harris County Adult Glioma Study, 2001-2006

	Controls (n = 600)	Cases (n = 325)	Odds ratio (95% CI)
Antihistamine use			
Yes	92	42	1.37 (0.87, 2.14)
No	508	278	Reference
Anti-inflammatory use			
Yes	188	72	0.67 (0.47, 0.96)
No	412	248	Reference
History of asthma or allergy			
Yes	202	44	0.34 (0.23, 0.51)
No	398	276	Reference
History of chickenpox			
Yes	515	236	0.52 (0.36, 0.75)
No	85	84	Reference
History of oral herpes			
Yes	76	10	0.28 (0.14, 0.57)
No	524	310	Reference
History of mononucleosis			
Yes	65	13	0.40 (0.21, 0.76)
No	535	307	Reference
History of migraine headaches			
Yes	50	4	0.19 (0.07, 0.54)
No	550	316	Reference
Previous head injury			
Yes	184	115	1.41 (1.03, 1.93)
No	416	205	Reference

NOTE: The odds ratios were derived from unconditional logistic regression models, adjusting for age, gender, and race, and controlling for all other covariates.

Controls, on average, were more highly educated, reported a history of alcohol use, and were more likely to report a positive history of the inflammation-related variables than cases (Table 1). After controlling for all other covariates in the multivariable model (listed in Table 2), the use of NSAID was associated with a 33% reduction in risk (odds ratio, 0.67; 95% CI: 0.47, 0.96), whereas the use of antihistamines was associated with a 37% increase in the risk for glioma (odds ratio, 1.37; 95% CI: 0.87, 2.14; Table 2). However, when antihistamine use was examined only among those reporting a history of asthma or allergies, a 3.56-fold increase in risk was seen for those who reported the longest (≥10 years) regular antihistamine use (Table 3).

History of inflammation-related events was asked of all participants (Table 1), including asthma or allergy, chickenpox or shingles, oral herpes, mononucleosis, migraine headaches, head injury, and stroke. Adjusted odds ratios for each inflammation-related event and medication use are presented in Table 2. A history of asthma or allergy was associated with a 66% reduction in the risk for glioma (odds ratio, 0.34; 95% CI: 0.23, 0.51). A history of chickenpox was associated with a 48% reduction in the risk for glioma (odds ratio, 0.52; 95% CI: 0.36, 0.75). A history of self-reported oral herpes was also associated with a decrease in the risk for glioma (odds ratio, 0.28; 95% CI: 0.14, 0.57); however, the number of exposed cases was low. Similarly, self-reported mononucleosis resulted in a 60% reduction in the risk for glioma (odds ratio, 0.40; 95% CI: 0.21, 0.76). Although the number of subjects reporting a history of migraine headache was low (50 controls and 4 cases), a significant reduction in risk (81%) was observed and the upper limit of the confidence interval remained well below 1.0 (odds ratio, 0.19; 95% CI: 0.07, 0.54). Previous head injury also showed a significant increase in risk (odds ratio, 1.41; 95% CI: 1.03, 1.93), although this could be because of recall bias.

Table 3. Adjusted odds ratios for the use of antihistamines stratified by history of asthma or allergies among glioma cases and controls, Harris County Adult Glioma Study, 2001-2006

Antihistamine use	Controls (n = 600)	Cases (n = 325)	Odds ratio (95% CI)
No asthma or allergy history			
No use	362	259	Reference
<10 y	21	14	0.91 (0.45, 1.84)
≥10 y	15	8	0.70 (0.29, 1.69)
Any use	36	22	0.82 (0.47, 1.44)
Any asthma or allergy history			
No use	146	23	Reference
<10 y	32	8	1.73 (0.69, 4.29)
≥10 y	24	13	3.56 (1.56, 8.14)
Any use	56	21	2.54 (1.28, 5.03)

NOTE: The odds ratios were derived from unconditional logistic regression models, adjusting for age, gender, and race.

Discussion

In our analysis, cases were more likely to report regular long-term use of antihistamines than controls, especially cases reporting a history of allergies or asthma, whereas the inverse was true for NSAID. Schlehofer et al. (6), in their report from a multinational study, found a 30% reduction in the risk for adult glioma with antihistamine use. A recent report in a United Kingdom population showed a slight but nonsignificant reduction in risk associated with ever use of antihistamines by those reporting hay fever, allergic rhinitis, or conjunctivitis (7). A related report from the Nordic-United Kingdom pooled study also found a nonsignificant 22% reduction in the risk of ever antihistamine use in those reporting hay fever (10). These reports could differ from the current findings because of the definition of long-term antihistamine use in the current study or because of differences in use of these drugs between the different study populations. In the report by Wigertz et al. (10), 51% of controls who reported hay fever took antihistamines compared with 48% of cases. In our study, 28% of controls who reported a history of asthma or allergies regularly took antihistamines compared with 48% of cases.

Our findings support a positive association for glioma in adults who were long-term users of antihistamines. Although there was a weak correlation (ρ = 0.2438) between history of asthma or allergies and antihistamine use, the inclusion of an interaction term (P = 0.02) in our model did not significantly alter the main effects for the other terms. Moreover, the addition of asthma or allergies to a main-effects model modified the effect of antihistamine use, and the largest effect in the stratified analysis was seen among those who reported a history of asthma or allergies and long-term use of antihistamines.

Studies have reported a protective effect of allergies or asthma on the development of several cancers, including gliomas (20). Fairly consistent risk reductions of 30% to 50% (similar to our current results) have been reported for glioma among those with a history of allergies or asthma in case-control and cohort studies from the United States (1, 3, 9), Europe (5-8, 10), and Australia (2, 4). Wiemels et al. (21) reported that immunoglobulin E levels, a measure of allergic response, were lower in adult glioma cases than controls (odds ratio, 0.37) and that early-onset allergies (before the age of 13 years) were more likely to be related to immunoglobulin E than late-onset allergies. Stronger support for a protective association with asthma is suggested by one study reporting that, compared with controls, cases were less likely to carry polymorphisms in the *IL4RA* and *IL13* genes that increase the risk for asthma and more likely to carry polymorphisms that decrease the risk for asthma (11). However, these findings were not replicated when the authors repeated their analysis in a larger pooled data set (12), and Turner et al. (22) were unable to show differences in brain tumor mortality among a cohort of asthma and hay fever suffers in the United States.

In a similar vein, Wrensch et al. (23) reported a 40% to 60% reduction in glioma risk associated with a history of chickenpox or shingles. We showed a 48% reduction in the risk for glioma associated with chickenpox infection. They also found that measured immunoglobulin G antibody levels against varicella-zoster virus were higher in controls than cases (23). We showed that self-reports of oral herpes lesions (herpes simplex virus) and mononucleosis (Epstein-Barr virus or Cytomegalovirus) were also higher among controls than cases. It is conceivable that the constant reactivation of these herpesviruses may increase immune surveillance and partially account for the decrease in risk associated with a history of infection.

The current study adds to a growing body of literature suggesting an increasing role of modulation of the immune system in the prevention or promotion of gliomas. We recognize that additional studies are needed to corroborate our findings for antihistamines. However, these medications cross the blood-brain barrier and can have significant sedative effects. The histamine H_1 receptors targeted by these drugs are found on glial cells and have been shown to stimulate proliferation in a receptor-dependent fashion (24). In addition, constitutive activation of H_1 receptors triggers numerous inflammation pathways such as nuclear factor κB and arachidonic acid, leading to the production of prostaglandins, leukotrienes, and cytokines (25). These substances, in turn, could drive inflammation even in the presence of antihistamines. Moreover, histamine itself is shown to exhibit both immune-stimulatory and -suppressive behavior when interacting with the H_1 receptor (26). This may explain the risk observed in the current study for the use of compounds that interfere with normal H_1 receptor activity. Lastly, one report showed that melanoma cells rich in H_1 receptors undergo intensive DNA damage and apoptosis in the presence of antihistamines (27). Such mechanisms could be important for glial cells that harbor high concentrations of H_1 receptors.

To our knowledge, this is the first report to investigate the association between adult glioma and antihistamine use in a U.S. population and to examine the joint effects of allergy or asthma with antihistamine use. A main limitation of the current study is the self-reported nature of the medications. In addition, most of our controls were interviewed by telephone whereas the interview method was split for the cases. This could introduce some information bias; however, response rates to the medication questions were similar in both groups regardless of the interview method. We also did not ask about specific types of allergies, nor did we collect data on dosage or indication for use. In future studies, we will gather detailed data on these aspects of use to allow a better understanding of the underlying mechanisms of antihistamines in glioma risk and to better understand differences in use of these drugs among allergy sufferers in our study population.

Another limitation of our study is the inability to adequately account for the time between beginning antihistamine use and the glioma diagnosis. Cases were instructed to report drugs taken before 6 months prior to their diagnosis; however, this could be difficult for them to remember. On the other hand, antihistamines are not usual drugs for the relief of symptoms commonly associated with brain tumor presentation (e.g., seizures, drowsiness, limb weakness, and changes in vision, speech, personality, or memory). Therefore, the initiation of antihistamine use as a result of an undiagnosed glioma is unlikely. Several epidemiologic studies corroborate the involvement of inflammatory factors in glioma development; however, the mechanisms are still poorly

understood because of the difficulty in studying such rare tumors. We are currently working to pool data with other investigators to examine these questions more closely.

Disclosure of Potential Conflicts of Interest

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