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Antihistamine use and immunoglobulin E levels in glioma risk and prognosis

E. Susan Amirian [a,b], Deborah Marquez-Do [a], Melissa L. Bondy [a,b], Michael E. Scheurer [a,b,*]

[a] Dan L. Duncan Cancer Center, Baylor College of Medicine, One Baylor Plaza MS:BCM305, Houston, TX 77030, USA
[b] Department of Pediatrics, Baylor College of Medicine, One Baylor Plaza MS:BCM305, Houston, TX 77030, USA

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ABSTRACT

Objective: An inverse association between personal history of allergies/asthma and glioma risk has been fairly consistently reported in the epidemiologic literature. However, the role of regular antihistamine use remains controversial due to a small number of studies reporting contradictory findings. We evaluated the association between regular use of oral antihistamines and glioma risk, adjusting for a number of relevant factors (e.g., immunoglobulin E levels and history of chickenpox). *Methods*: We used a subset of the Harris County Case-Control Study, which included 362 pathologically confirmed glioma cases and 462 cancer-free controls, to evaluate this association using unconditional multivariable logistic regression. These models were run among the overall study population and stratified by allergy status. Cox regression was utilized to examine whether antihistamine use was associated with mortality among all cases and separately among high-grade cases. *Results*: Antihistamine use was strongly associated with glioma risk among those with a positive allergy/asthma history (OR: 4.19, 95% CI: 2.06–8.51), but not among those with a negative history (OR: 1.59, 95% CI: 0.95–2.67). There were no significant associations between antihistamine use and survival among cases. *Conclusion*: The current study implies that regular antihistamine use may increase glioma risk. However, several larger studies are necessary before definitive conclusions can be drawn.

1. Introduction

Glioma is a highly fatal disease with few confirmed risk factors [1,2]. However, recent studies have associated glioma susceptibility with factors that either modulate the immune response or serve as a surrogate for immune dysfunction (e.g., polymorphisms in immune genes, immunoglobulin E (IgE) levels, atopic conditions, antihistamine use) [3–19]. A meta-analysis of numerous case-control and two cohort studies has indicated that there is an inverse association between history of atopy/allergies and glioma risk that is unlikely to be due to chance alone [20]. Cumulatively, such findings on allergy status, in combination with the existing literature on other immunomodulatory factors, strongly support the involvement of immune hyperactivity or atopy in predicting glioma susceptibility. By contrast, the effects of regular use of antihistamines, which are commonly taken to counteract symptoms associated with allergies and atopic conditions, remain unclear.

Although a possible link between cancer risk and the use of antihistamines has long been suspected [21], results from epidemiological studies investigating such associations have not yet reached a consensus [11,12,22–28]. In addition to their immunomodulatory capabilities, another reason for suspecting the potential involvement of common antihistamines in carcinogenic processes is their structural similarity to N,N-diethyl-2-[4-(phenylmethyl) phenoxy]ethanamine HCl (DPPE), which is an intracellular histamine antagonist related to tamoxifen that has been shown to promote tumor growth [26]. Also of concern, particularly with regard to brain tumor etiology, is that antihistamines, many of which are capable of crossing the blood–brain barrier, may induce nitrosatable exposures in the brain [11,25]. Therefore, the potential impact of long-term antihistamine use strongly warrants clarification, because, in addition to their interference with histamine-regulated pathways, there are several other mechanisms by which these medications could potentially influence cancer risk. The purpose of this study was to evaluate the impact of regular oral antihistamine use in a population of 362 pathologically confirmed glioma cases and 462 cancer-free controls from the Harris County Case-Control Study (HCCCS).

* Corresponding author at: One Baylor Plaza MS:BCM305, Houston, TX 77030, USA. Tel.: +1 713 798 5547; fax: +1 713 798 8711.
E-mail addresses: amirian@bcm.edu (E.S. Amirian), deboraha@bcm.edu (D. Marquez-Do), mbondy@bcm.edu (M.L. Bondy), Scheurer@bcm.edu (M.E. Scheurer).

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2. Methods

2.1. Study population and data collection

Detailed information on the HCCCS can be found elsewhere [11]. Briefly, newly diagnosed, histologically confirmed glioma (ICD-O-3 codes 9380-9481) cases over the age of 18 were identified between 2001 and 2006 by hospital physicians in and around Harris County, Texas. A study neuropathologist conducted central review of pathology specimens to confirm glioma diagnosis. Cancer-free controls were obtained through random-digit dialing using standard methods [29,30], and were frequency-matched to cases on age (±5 years) and sex. The ability to speak English was an eligibility criterion. Participation rates for the parent study were 77% and 53% for cases and controls, respectively. Despite efforts to frequency match at recruitment, the study population had to be re-matched on sex in the analysis phase. This was likely due to the higher incidence of glioma among males [31], in conjunction with a higher availability of female controls. Thus, only a subset of available controls was utilized in the final analyses.

Data on demographic factors, health characteristics, and familial attributes were obtained through structured questionnaires, which were administered as in-person or telephone interviews. Interviews with the cases were conducted before radiotherapy or chemotherapy, but normally after surgery. Information on allergies and/or asthma, history of chicken pox, and oral antihistamine use was self-reported during the interviews. With regard to the medication use data, subjects were provided a list of drugs (i.e., generic and brand names of antihistamines) and were asked whether they had taken any of the drugs on a regular basis for at least six consecutive months before diagnosis or time of interview (for cases and controls, respectively). If the participant reported regular use, they asked the specific name of the drug(s) and the duration of regular use. No dose information was collected. Response rates to the medication questions among cases and controls were not significantly different between in-person or telephone interviews. Additionally, samples of venous blood (20 mL) were collected from each participant (for cases, before chemotherapy or radiation therapy). The parent study was approved by the MD Anderson Cancer Center Institutional Review Board (IRB) and written informed consent was obtained from all participants. The current analysis was also approved by the Baylor College of Medicine IRB.

2.2. Serology

IgE levels were determined from the participants' blood samples taken at the time of enrollment into the study. Standardized IgE enzyme-linked immunosorbent assay (ELISA) kits (Calbiotech, Spring Valley, CA) were utilized to determine IgE levels, according to manufacturer's instructions. This assay provides a quantitative assessment of IgE in serum on the basis of a standard curve with six standard values. Laboratory personnel were blinded to case-control status during the laboratory analyses.

2.3. Statistical analysis

Cases and controls were compared on matching characteristics and other relevant attributes using χ^2 tests. Unconditional logistic regression models were used to calculate odds ratios and 95% confidence intervals (CI) for the associations between glioma status and regular oral antihistamine use, adjusting for potential confounders (which were chosen *a priori*). History of chickenpox was included in our models as a potential confounder because a growing body of literature indicates that varicella-zoster exposure may be relevant to glioma risk [32–35] and may also potentially impact the risk for atopic conditions [36,37]. The regression models were run both among the overall study population and stratified by self-reported allergy/asthma status, as antihistamines are sometimes taken regularly for indications other than allergic conditions (i.e., as sleep aids or antiemetics). All multivariable models included matching characteristics, in order to control for residual confounding, and post hoc analyses were conducted with all available controls to assess how much re-matching on sex in the analysis phase of our study affected logistic regression results.

IgE levels were included in the models dichotomously ($\geq$ or $<$250 international units [IU] per mL), because the impact of controlling for IgE levels at enrollment was similar whether adjusted for dichotomously, continuously, or as a three-level variable (data not shown). Several possible cut-points for IgE levels were explored, with some dichotomizing male and female "normal" levels differently. However, despite the use of several exploratory cut-points, the minute extent to which adjustment for IgE impacted the odds ratio for antihistamine use was not affected, and the odds ratio for IgE never reached statistical significance.

Cox proportional hazards regression models were utilized to assess whether regular oral antihistamine use was associated with mortality risk among all cases, and separately, among high-grade (WHO grade IV) glioma cases. Cancer-directed treatment was not adjusted for, as treatment-related variables are unlikely to be associated with history of antihistamine use reported at enrollment, and therefore, would not act as data-based confounders. Survival analyses could not be stratified by self-reported allergy/asthma status due to the small numbers of cases resulting in inadequate statistical power (only 53 total cases with positive history of allergies/asthma). Log–log plots were used to evaluate the proportional hazards assumption; no violations were noted. All *p*-values were two-sided with a 0.05 level of significance, and all statistical analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC).

3. Results

The distribution of matching characteristics and other attributes among glioma cases ($n = 362$) and cancer-free controls ($n = 462$) is presented in Table 1. There were no statistically significant differences between cases and controls in sex, age, or IgE levels. However, significantly higher proportions of controls reported positive histories for allergies/asthma and chickenpox, compared to cases.

Approximately 19% of cases ($n = 67$) and 15% of controls ($n = 70$) reported regular antihistamine use. Of the 53 cases who reported a positive history of allergies/asthma, 27 (51%) reported regular antihistamine use; whereas among the 162 controls reporting allergies, 41 (25%) reported regular use. Among cases with a negative history of allergies/asthma, 13% ($n = 40$) reported regular antihistamine use, compared to almost 10% ($n = 29$) of controls without allergies/asthma.

In the overall logistic regression model (Table 2), regular oral antihistamine use was significantly associated with glioma status (OR: 2.15, 95% CI: 1.42–3.25), adjusting for allergies/asthma, history of chickenpox, IgE levels, sex, age, and race. By contrast, self-reported allergies/asthma and chickenpox were both inversely associated with glioma risk (OR: 0.28, 95% CI: 0.20–0.41, and OR: 0.49, 95% CI: 0.34–0.71, respectively). When stratified by allergy/asthma status, antihistamine use remained strongly associated with glioma risk among those with a positive allergy/asthma history (OR: 4.19, 95% CI: 2.06–8.51), but not among those with a negative history (OR: 1.59, 95% CI: 0.95–2.67). In the group that did not report having allergies/asthma, history of chickenpox was significantly protective against glioma risk (OR: 0.39, 95% CI: 0.26–0.60), but this association did not hold among those who did report