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HISTORY OF ALLERGIES AMONG ADULTS WITH GLIOMA AND CONTROLS

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The causes of most adult gliomas are essentially unknown. Previous studies have indicated associations between immune system factors and the incidence of adult glioma, specifically that those individuals with certain allergic conditions may have decreased risk of glioma. We obtained detailed allergy histories for 405 adults newly diagnosed with glioma in the San Francisco Bay Area from 1997–1999 and 402 age-gender-ethnicity frequency-matched population-based controls. Seventy-nine percent of eligible cases or their proxies and 74% of eligible controls completed in-person interviews about allergies, age at onset, frequency, duration and severity. Overall, cases were less likely than controls to report any allergy (72% *vs.* 85%; odds ratio [OR] = 0.5 [0.3–0.7]); for self-reported cases (n = 269), OR = 0.7 (0.4–0.97) and for proxy-reported cases, OR = 0.3 (0.2–0.5). Pollen, dairy and nut allergies were significantly less common in cases than controls and most other allergens had odds ratios of less than one. There were no apparent trends with numbers of symptoms, route of exposure of allergen or reported severity of allergy, but there was a significant dose-response with increasing numbers of allergens ($p < 0.0001$ for linear trend among all cases *vs.* controls and $p = 0.02$ among self-reported cases only *vs.* controls). Although our work displays strong and consistent associations, future efforts must attempt to establish whether an immune system typified by proclivity to allergies, or an immunologic consequence of the allergies themselves, might be capable of preventing nascent brain tumors. The dominance of humoral immunity in the central nervous system is consistent with either of these models. Alternatively, common genetic or environmental causes for allergies and gliomagenesis may mediate or confound these observed inverse risks for allergies and gliomas, or other explanations may exist. Future work might reveal an important role for immunologic factors in gliomagenesis and potential preventative and/or therapeutic modalities.

Key words: *allergy; glioma; brain cancer; case-control study*

Epidemiologic studies have not identified consistent causal risk factors for the majority of adult-onset glioma, although a multifactorial etiology that includes a role for common genetic susceptibility loci is likely.[1–3] Also, the possibility of different causes for different histologic and molecular subtypes of tumors must be considered.[4] The detection of viruses and viral proteins in clinical brain tumor samples[5,6] has focused attention on the possible involvement of infectious agents in the etiology of glioma. In our previous population-based epidemiologic studies, we demonstrated an inverse association between the occurrence of glioma with self-reported history of chicken pox and shingles and serologic immunity to the neurotropic virus Varicella Zoster.[7,8] Interestingly, there was no association of glioma observed for Epstein Barr virus, Cytomegalovirus or Herpes Simplex I/II virus, the latter like Varicella being neurotropic.

The associations of glioma with the presence of viral agents or humoral immunity to viruses could be evidence of impaired immunosurveillance. Indeed glioma patients have long been known to demonstrate distinct deficits in immune function, however, these defects primarily disrupt cell-mediated immunity.[9] Immunosuppression in glioma patients has been attributed to the secretion of soluble factors that inhibit T-cell and monocyte function[10,11] but is not thought to affect humoral or T-cell-independent immune responses. In fact, total serum IgG levels in glioma patients were not significantly lower than those found among healthy persons in a study in India[12] and (as indicated above) we previously found IgG levels of several viruses apart from Varicella in glioma patients were not different from age-, gender- and ethnicity-matched controls.[7,8] It is currently unclear whether the cell-mediated immune defects that have been studied extensively in patients at diagnosis play a role in the early stages of gliomagenesis. The brain is traditionally thought of as an "immune privileged" organ,[13] however, it is now known that the brain is capable of supporting vigorous and highly coordinated immune responses to intrathecal neoantigens.[14] Hence, either cell-mediated or humoral immunity could influence the development and early growth of brain tumor cells.

Indirect support for an association of glioma risk and humoral immunity has come from epidemiologic studies that suggest a role for reported history of allergy and certain infectious diseases with glioma as well as other cancers.[15–18] Although we did not directly explore the nature of a patient's immune system prior to diagnosis of glioma, we have explored one aspect of immune-system function via questionnaire information—namely, history of allergies. We asked about such history because of a suggestive report showing an inverse relationship between glioma patients and controls of specific immunologic factors including history of allergies.[19] This study was later published within an international study of nearly 1,200 glioma and 300 meningioma cases and 2,500 controls that showed an inverse association (odds ratio [OR] = 0.6, 95% confidence interval [CI]: 0.5–0.7) between glioma (but not meningioma) and allergic diseases.[17] This inverse association between history of allergy and gliomas also was recently replicated in another multicenter study in the United States.[18] In our study, we included a wide variety of questions about the history of allergies in a population-based series of adult cases and controls in the San Francisco Adult Glioma Study in an attempt to confirm and better characterize the association. Our analysis confirms the previous reports of an inverse relationship between allergies and adult glioma, provides some clues to the specificity (regarding type of allergy and symptom), magnitude and potential mechanism of this association and suggests directions for future research.

MATERIAL AND METHODS

Case and control ascertainment

Our study attempted to enroll all adults newly diagnosed with glioma (*International Classification of Disease for Oncology*,[20]

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morphology codes 9380-9481), in the 6-county San Francisco Bay Area from May 1997 to August 1999. Cases were ascertained within 2–8 weeks of diagnosis using the Northern California Cancer Center's rapid case ascertainment system with a protocol as previously described.[21] Controls were identified using random digit dialing methods and age-gender-ethnicity frequency matched to cases using a protocol similar to that previously described.[21] All study protocols were reviewed and approved by the Committee on Human Research at the University of California, San Francisco, CA.

Interviews

In-person interviews with cases (or their proxies) and controls lasted approximately 2 hr and used a structured questionnaire and show cards. Subjects were offered a brief telephone interview if they declined the full in-person interview.

The questionnaire asked extensive information about family and personal medical history including allergies, demography, occupational history, X-ray exposures, drugs, diet, injuries and other personal information including smoking. Detailed information regarding history of allergies was collected in tabular form on 6 questionnaire pages. Data were collected for the following allergens: house dust, mold or mildew, pollens, poison oak/ivy, stinging or biting insects, eggs, dairy, shellfish, wheat, nuts, other foods, cats, dogs, other animals, prescription and nonprescription drugs, soap/detergents and cosmetics. Additional spaces were included in the questionnaire for "other" items that the patient identified as allergens but were not specifically asked for by name by the interviewer. Interviewers prompted subjects with show cards for each of the general allergen categories and first asked (yes/no/don't know) whether the allergens produced any of the following symptoms (runny nose, burning/watery eyes, sneezing/congestion, wheezing/asthma, rash/hives, itching, swelling/inflammation, nausea/vomiting, diarrhea, headaches, anaphylactic shock, other: specify). If the respondent answered yes to any symptom to an allergen, the interviewer checked which symptoms, then asked how old the individual was when first experiencing any symptom to the allergen and whether or not this allergy was still present. If the allergy no longer existed, the subject was asked how many years altogether the allergy with its associated symptom(s) lasted. In addition, frequency of the allergy was asked as how many days/year or weeks/year and lifetime episodes were experienced. If these 3 frequency categories did not fit, the subject was prompted to supply a description of the frequency. Finally, the maximum severity of the allergic episodes for each allergen was assessed by 1 of the 4 following categories: mild (no medication taken); moderate (uses prescription or nonprescription medication sometimes); severe (medical care required or under regular medical care); don't know. The brief telephone interview (for those who refused an in-person interview) also included some allergy history information.

Statistical methods

Odds ratios (OR) for cases *vs.* controls that reported history of allergic conditions were estimated with logistic regression, controlling for age, gender and ethnicity (white/nonwhite). ORs were estimated for all cases *vs.* controls, self-reporting cases *vs.* controls and proxy-reported cases *vs.* controls. ORs also were computed for individual reported allergens, reported symptoms, allergy severity and to the likely route of allergen exposure. Three route categories were chosen: respiratory (house dust, molds, pollens, cats, dogs and other animals), digestive (eggs, dairy, shellfish, wheat, nuts including peanuts/cashews and other foods) and dermal (poison oak, insect stings/bites, soap and cosmetics). Where an allergen was involved in more than 1 route, it was grouped in its major route of exposure. Simple descriptive statistics comparing participants and nonparticipants were conducted with SAS.[22] The statistical program PROC LOGISTIC (SAS) was used for computations of ORs.[22]

Control for potential bias and confounders. A common difficulty for retrospective interview studies is the potential for reporting bias; that is, patients with disease might be more or less likely to recall, to fabricate or to be prompted by interviewers to supply information that might have contributed to the etiology of their disease. This seems unlikely to happen for history of allergies, which would not be commonly thought to affect glioma, or if they were, might be thought to be positively associated rather than negatively. Another bias could come from an estimate of lifetime incidence of allergy that may be biased by the age of the individual—older individuals providing less accurate information. Also, proxies might be less likely to know of and report temporally distant or minor allergies. To help control for these potential biases, ORs were adjusted for age, gender and ethnicity, and results emphasize associations for self-reported cases. ORs were also adjusted for maternal age and smoking since these are additional factors that might be associated with incidence of allergic disease such as asthma.[23] ORs were also adjusted by socioeconomic status indicators including income and education level attained (college degree/no college degree). Finally, to control for potential confounders, ORs were computed for route of exposure and allergen stratifying by tumor histopathology (glioblastoma or other glioma histologies) and by self/proxy status.

RESULTS

Ascertainment of cases and controls

A total of 405 of 511 (79.3%) eligible cases identified through rapid case ascertainment consented to the long questionnaire, and an additional 23 (4.5%) consented to the short telephone questionnaire only (Table I). A total of 402 of 541 eligible controls (78.3%) identified by random digit dialing (RDD) consented to the full interview with another 68 (12.6%) agreeing to the brief telephone interview. Additional details of the specific reasons for subject exclusion and the distribution of RDD calls are included in Table I.

TABLE I – CASE AND CONTROL ASCERTAINMENT AND PARTICIPATION: THE SAN FRANCISCO BAY AREA ADULT GLIOMA STUDY, 1997–1999

	Cases n[1]	Controls n[1]	Distribution of RDD calls	n[1]	%[2]
Full interview	405	402	Not in service	1,591	17.1
Accepted brief telephone interview only	23	68	Business line	1,218	13.1
Refused to enter study	53	49	Fax/modem	700	7.5
Language problem	6	3	No response after 10 calls	1,417	15.3
Too ill for interview	1	3	Refusals	1,541	16.6
Inability to locate subject	21	16	Language or health problems	559	6
Refused by patient's practitioner	2		Multiple lines	73	0.8
Totals	511 (79.3%[4])	541 (74.3%[4])	Too young	24	0.3
			Quota full	1,513	16.3
			Ineligible	80	0.9
			Good match[3]	562	6.1
			Out of area	4	0

[1]Number of subjects in category.–[2]Percent of total RDD calls.–[3]Of 562 good matches from RDD, the study closed before contacting 20 and 1 proved to be related to a case, thus there were 541 eligible controls.–[4]Percent with full interview of those eligible.

The average age for cases was 56.0 ± 0.8 (SE) years and controls 55.3 ± 0.8 (Table II). Nonparticipants were only slightly older for both cases (60 years) and controls (57 years). The proxy- and self-reported cases did not significantly differ from each other by ethnicity, gender or years of total education (Table II), but proxy-reported cases were significantly older than self-reported cases (means 65 *vs.* 51 years, respectively $p < 0.001$), were more likely to have a college degree and were more likely to have been diagnosed with glioblastoma multiformae (GBM, 79% *vs.* 48%, respectively, $p < 0.001$).

Allergy and glioma

Overall results for any allergy demonstrated a significant deficit of reported allergies among glioma patients when compared to controls (OR = 0.47, 95% CI: 0.33—0.67, Table III) and among self-reported cases (OR = 0.65, 95% CI: 0.43–0.97). When adding in those cases and controls who answered only the short phone questionnaire, the associations were barely affected (all glioma cases *vs.* controls, OR = 0.55, 95% CI: 0.40–0.75; self-reported *vs.* controls, OR = 0.66, 95% CI: 0.47–0.95). These and all other reported ORs were adjusted for age, gender and ethnicity (white/nonwhite). This adjustment did not fundamentally alter any result, and therefore unadjusted ORs are not reported. We also ran models adjusting for other potentially confounding variables but found that none altered the ORs by more than 2% and therefore are not reported. These adjustments include smoking, maternal age, income (as categorical and continuous variable in separate models) and education (college degree/no college degree).

In an attempt to define or specify what characteristics of allergies differed between cases and controls, ORs were computed for specific allergens, reported allergy symptoms, as well as grouping reported symptoms into putative "routes of exposure" including respiratory, digestive and dermal. ORs for specific allergens were highly variable (Table IV), although for high-frequency allergen categories (>100 subjects among cases and controls), including house dust, pollens, poison oak, stings and cats, ORs narrowly ranged from 0.73–0.94 for self-reported cases (Table IV). Some individual low-frequency allergies were highly inversely associated with case status, particularly among food allergens (self-reported, dairy OR = 0.48; wheat OR = 0.15; nut OR = 0.32, Table IV). An assessment of dose-response was also calculated by grouping individuals by numbers of allergy (*i.e.,* by reported allergen) into 5 "dose" categories and calculating ORs compared to those who reported no allergies as a reference (Table V). Interestingly, ORs tended to diverge further from the null in subjects with increasing numbers of allergies ($p < 0.0001$ for linear trend). This trend was also significant among self-reported cases only ($p = 0.02$ for linear trend).

Regarding individual symptoms regardless of allergen, ORs of less than 1 were demonstrated for all symptoms, but significantly (*i.e.,* 95% CIs exclude 1) for runny nose, watery eyes, sneezing, wheezing, itching, swelling, headaches, anaphylactic shock and other symptoms (Table VI). The only significant ORs for symptoms among self-reported cases *vs.* controls were sneezing, wheezing and anaphylactic shock (Table VI), but all ORs for all symptoms for self-reported cases *vs.* controls except for that of symptoms of "rash or hives" were less than 1. The relative lack of specificity by type of allergen was also apparent when allergens were grouped by route of exposure: respiratory allergens (OR = 0.62, 95% CI: 0.47–0.82), digestive allergens (OR = 0.55, 95% CI: 0.38–0.81) and dermal (OR = 0.58, 95% CI: 0.44–0.78). Among the self-reported cases only, ORs by route of exposure were also equivalent but slightly higher and only the respiratory allergen subgroup had CIs that did not cross 1: respiratory allergens (OR = 0.70, 95% CI: 0.51–0.96), digestive allergens (OR = 0.67, 95% CI: 0.44–1.02) and dermal allergens (OR = 0.78, 95% CI: 0.57–1.07).

The allergy assessment also included a measure of severity by 3 levels (see Material and Methods). Using individuals who reported no allergies of any kind as a reference, ORs were calculated for each reported severity level (Table VII). ORs were less than 1 at all 3 severity levels and lowest among "mild" severity for all cases and also for self-reported cases *vs.* controls. Interestingly, among the self-reported cases, the CI excluded 1 for only "mild" severity (OR = 0.52; 95% CI: 0.31–0.86).

Assessment of bias: age and tumor histology

Proxy-reported cases invariably showed stronger and more significant inverse associations with reporting of allergies than self-reported cases (Table III). Proxy-reported cases are significantly older and more likely to be diagnosed with GBM than self-reported cases (Table II), presenting the possibility that the inverse association of glioma with allergies could be age- or pathology-specific. On the other hand, proxies might systematically underreport allergies at a higher rate than self, a simple reporting bias. To assess this to the degree that our data allowed, we divided self- and proxy-reported cases into GBM and non-GBM histopathologies and calculated case-control ORs for allergies for these subgroups of cases. The inverse associations of glioma with allergies were present for both GBM and other histologies and among both self- and proxy-reported cases (Table VIII). Based on small numbers, ORs were strongest for proxy-reported non-GBM cases *vs.* controls (note that these were younger on average, mean age 60, than proxy-reported GBMs, mean age 66). ORs for self-reported cases with non-GBM histologies were also significantly associated with allergies, but CIs for self-reporting cases with GBMs include 1 (Table VIII). Further stratification by age did not indicate variable associations within GBM/non-GBM histologies (data not shown).

TABLE II – – DESCRIPTION OF PARTICIPANTS *VS.* NONPARTICIPANTS: AGE, GENDER, ETHNICITY, EDUCATION AND INCOME: THE SAN FRANCISCO BAY AREA ADULT GLIOMA STUDY, 1997–1999

	Participants				Nonparticipants	
	All cases (n = 405)	Self-reporting cases (n = 269)	Proxy-reported cases (n = 136)	Controls (n = 402)	Cases (n = 106)	Controls (n = 139)
Mean age + SE	56.0 ± 0.8	51.3 ± 0.9[1]	65.1 ± 1.2[1]	55.3 ± 0.8	59.6 ± 1.6	57.1 ± 1.3
% White	82.2	82.5	81.6	83.1	nc[2]	nc[2]
% Male	55.3	55.4	55.2	54	63.2	59.0
% Glioblastoma	58	47.6[1]	78.7[1]	—	70.8	—
% College graduate	53.3	59.5[1]	41.2[1]	58.2	26.1[3]	54.4[3]
Mean education (years)	14.5 ± 3.3	15.1 ± 3.2	13.5 ± 3.3	15.0 ± 3.3	nc[2]	nc[2]
Household income (USD/year)						
≤$29,999 (%)	21.8	14.8	36.0	22.6		
$30–49,999 (%)	23.1	22.3	24.8	20.0		
$50–69,999 (%)	17.3	17.2	17.6	18.5	nc[2]	nc[2]
$70–99,999 (%)	15.0	18.4	8.0	18.8		
$100,000 + (%)	22.8	27.3	13.6	20.1		

[1]p-value < 0.001 self vs. proxy.–[2]nc, data not collected.–[3]Based on only 23 respondents for cases and 68 respondents for controls.

TABLE III – ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR GLIOMA CASES AND CONTROLS WHO REPORTED HAVING ALLERGIES TO ANY OF THE ALLERGENS *VS.* REPORTING NO ALLERGIES: THE SAN FRANCISCO BAY AREA ADULT GLIOMA STUDY, 1997–1999

Allergy	%[1]	#[2]	n[3]	OR[4]	95% CI
Controls	84.6	340	402	Reference	
All cases	72.1	292	405	0.47	0.33–0.67
Proxy-reported cases	59.6	81	136	0.31	0.20–0.49
Self-reported cases	78.4	211	269	0.65	0.43–0.97

[1]Percent reporting a history of allergy.–[2]Number of subjects reporting any allergy history.–[3]Total number of subjects included in study.–[4]Case-control odds ratios adjusted for age, gender and ethnicity (white/nonwhite).

TABLE IV – FREQUENCIES OF SUBJECTS REPORTING ALLERGY TO SPECIFIC ALLERGENS, WITH ASSOCIATED CASE-CONTROL ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI): THE SAN FRANCISCO BAY AREA ADULT GLIOMA STUDY, 1997–1999

Allergens	Controls			All cases					Self-reported cases				
	%[1]	#[2]	n[3]	%[1]	#[2]	n[3]	OR[4]	95%CI	%[1]	#[2]	n[3]	OR[4]	95% CI
House dust	22.7	88	388	17.2	69	401	0.72	0.50–1.03	21.4	57	267	0.86	0.58–1.26
Molds	12.4	48	388	9.3	37	398	0.73	0.46–1.16	10.9	29	266	0.81	0.49–1.36
Pollens	46.2	184	398	34.5	138	400	0.61	0.46–0.82	39.3	105	267	0.73	0.53–1.00
Cats	17.5	70	399	13.3	54	405	0.74	0.50–1.09	16.0	43	269	0.78	0.51–1.20
Dogs	6.0	24	399	6.4	26	404	1.09	0.61–1.94	7.4	20	269	1.14	0.61–2.13
Eggs	1.5	6	398	1.7	7	405	1.15	0.38–3.46	1.9	5	269	1.19	0.36–3.95
Dairy	10.1	40	395	4.2	17	401	0.40	0.22–0.71	5.3	14	266	0.48	0.25–0.90
Shelfish	5.0	20	398	4.2	17	405	0.83	0.43–1.61	3.7	10	269	0.76	0.35–1.67
Wheat	2.3	9	397	0.3	1	404	0.11	0.01–0.88	0.4	1	268	0.15	0.02–1.21
Nuts[5]	3.8	15	398	1.0	4	405	0.26	0.09–0.79	1.5	4	269	0.32	0.10–0.99
Any drugs	30.7	123	401	28.1	112	399	0.89	0.65–1.21	30.6	82	268	1.07	0.75–1.50
Poison oak	30.6	122	399	24.2	96	397	0.72	0.52–0.99	29.3	78	266	0.94	0.67–1.34
Stings (insects)	18.6	74	398	14.4	57	396	0.74	0.51–1.09	17.5	46	263	0.88	0.58–1.33
Soap	11.2	45	401	7.9	32	404	0.69	0.43–1.11	8.6	23	268	0.72	0.42–1.22
Cosmetics	10.0	40	400	5.9	24	404	0.57	0.34–0.97	6.3	17	268	0.64	0.35–1.16
Any other	33.1	133	402	24.7	100	405	0.67	0.49–0.91	27.5	74	269	0.78	0.55–1.10

[1]Percent reporting allergy history to specified allergen.–[2]Number of subjects reporting allergy history to specified allergen.–[3]Total number of subjects reporting on history of allergy to allergen (either yes or no).–[4]Case-control odds ratios adjusted for age, gender and ethnicity (white/nonwhite) and compares those with *vs.* those without reaction to the specific allergen.–[5]Nuts include nut-like legumes (peanuts and cashews).

TABLE V – ODDS RATIOS (OR) FOR "DOSE" OF ALLERGIES BY REPORTED SPECIFIC ALLERGENS, WITH ASSOCIATED CASE-CONTROL ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI): THE SAN FRANCISCO BAY AREA ADULT GLIOMA STUDY, 1997–1999

No. of allergens reported	Controls (n = 402)		All cases (n = 405)				Self-reported cases (n = 269)			
	%[1]	#[2]	%[1]	#[2]	OR[3]	95% CI	%[1]	#[2]	OR[3]	95% CI
0	15.4	62	27.9	113	1.0 (reference)		21.6	58	1.0 (reference)	
1	20.2	81	22.2	90	0.61	0.4–0.94	22.3	60	0.78	0.47–1.27
2	19.1	77	16.3	66	0.47	0.3–0.74	17.8	48	0.66	0.40–1.11
3	13.9	56	11.4	46	0.45	0.27–0.75	11.9	32	0.61	0.34–1.07
4	8.0	32	6.7	27	0.46	0.25–0.84	7.1	19	0.60	0.40–1.18
≥5	23.4	94	15.6	63	0.37	0.23–0.58	19.3	52	0.56	0.34–0.93
			$p < 0.0001$ for linear trend				$p = 0.02$ for linear trend			

[1]Percent reporting a history of allergy to specified number of allergens.–[2]Number of subjects reporting history of allergy to specified number of allergens.–[3]Case-control odds ratios adjusted for age, gender and ethnicity (white/nonwhite).

DISCUSSION

In our population-based study of incident glioma cases and controls, we found consistent inverse associations for both self- and proxy-reported histories of allergic conditions with the occurrence of adult glioma. Previously, a single published study considered the relationship of allergies and asthma to glioma; this study was published in part[19] and subsequently as a multicenter study.[17] Approximately the same risk ratios (*e.g.,* 0.5–0.7) as our current study were found in the multicenter study, these ratios being evident in 7 of the 8 study centers including 6 different countries. It is important to note that different definitions and greatly different frequencies of allergies were reported in our study and that of Schlehofer *et al.*[17,19] In the multicenter study, allergic diseases were assessed with the question: "Were you ever told by a doctor that you had (asthma, eczema, other allergies)?" This approach yielded an allergy prevalence of 20–31% at the various centers.[17] Our definition of allergy included mild through severe self-assessed allergic symptoms, yielding an overall prevalence of 85% in controls (Table III). It is likely that most of the subjects defined as having a history of allergies in the Schlehofer *et al.* study would have scored as "severe" (27–30% of our subjects) or "moderate" (an additional 26–30% of our subjects) in our study, however, direct comparisons are impossible. Interestingly, we found the strongest inverse association of allergy and glioma in comparisons of the category of least severe allergic symptoms (mild symptoms, managed without the care of a doctor, 17–24%, Table VII), consisting of many subjects that would presumably have not been included in the Schlehoffer *et al.* study. In apparent contrast, subjects reporting more allergies (without regard to severity) tended to have stronger inverse associations between allergy and glioma (Table V). Clearly, the difficulty in comparing the results of these 2 studies underscores the need for distinct medical and biologic definitions of allergic disease in future studies.

TABLE VI – FREQUENCIES AND CASE-CONTROL ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR REPORTING SPECIFIED SYMPTOM TO ANY ALLERGEN *VS.* THOSE EITHER NOT REPORTING SYMPTOM OR REPORTING NO ALLERGIES: THE SAN FRANCISCO BAY AREA ADULT GLIOMA STUDY, 1997–1999

Symptoms	Controls (n = 402)		All cases (n = 405)				Self-reported cases (n = 269)			
	%[1]	#[2]	%[1]	#[2]	OR[3]	95% CI	%[1]	#[2]	OR[3]	95% CI
Runny nose	41.3	166	31.6	128	0.66	0.49–0.88	36.8	99	0.79	0.57–1.08
Watery eyes	40.6	163	30.9	125	0.66	0.49–0.88	36.4	98	0.78	0.57–1.08
Sneezing	47.0	189	34.8	141	0.60	0.45–0.80	38.3	103	0.64	0.46–0.88
Wheezing	17.4	70	10.6	43	0.57	0.38–0.86	11.5	31	0.58	0.37–0.92
Rash/hives	48.3	194	44.0	178	0.85	0.64–1.12	49.4	133	1.03	0.76–1.41
Itching	50.3	202	38.3	155	0.62	0.47–0.82	46.5	125	0.85	0.62–1.16
Swelling	34.8	140	24.4	99	0.61	0.45–0.83	29.4	79	0.75	0.54–1.06
Nausea	15.2	61	11.1	45	0.70	0.46–1.07	11.9	32	0.77	0.48–1.23
Diarrhea	7.5	30	4.2	17	0.55	0.30–1.00	4.5	12	0.60	0.30–1.20
Headaches	16.2	65	10.4	42	0.61	0.40–0.92	11.5	31	0.65	0.41–1.03
Anaphylactic shock	4.0	16	1.0	4	0.24	0.08–0.73	0.4	1	0.09	0.01–0.65
Other	18.7	75	13.3	54	0.67	0.45–0.98	16.0	43	0.87	0.57–1.34

[1]Percent reporting symptom.–[2]Number of subjects reporting allergy symptom.–[3]Case-control odds ratios adjusted for age, gender and ethnicity (white/nonwhite).

TABLE VII – ADJUSTED ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR "SEVERITY" CATEGORIES FOR THOSE REPORTING ALLERGIES *VS.* THOSE WHO REPORTED NO ALLERGIES: THE SAN FRANCISCO BAY AREA GLIOMA STUDY, 1997–1999

Severity[1]	Controls (total n = 402)		All cases (n = 405)				Self-reported cases (n = 269)			
	%[2]	#[3]	%[2]	#[3]	OR[4]	95% CI	%[2]	#[3]	OR[4]	95% CI
None	15.4	62	27.9	113	1.00		21.6	58	1.00	
Mild	24.4	98	17.8	72	0.40	0.26–0.63	17.2	49	0.53	0.32–0.87
Moderate	29.9	120	25.7	104	0.48	0.32–0.72	30.5	82	0.70	0.44–1.10
Severe	29.6	119	27.2	110	0.51	0.34–0.77	29.4	79	0.70	0.44–1.12

[1]None, subjects reporting no allergy history; mild, no medications taken; moderate, prescription or nonprescription medications taken sometimes; severe, medical care required or under regular medical care.–[2]Percent reporting specific symptom severity.–[3]Number of subjects reporting.–[4]Case-control odds ratios adjusted for age, gender and ethnicity (white/nonwhite).

The overall consistency of our result with Schlehofer *et al.*[17] is a good argument against recall bias as a likely explanation for the inverse association of allergy with glioma, however, the multicenter study did not distinguish between results of proxy- and self-reported interviews, which we have seen produce somewhat different point estimates of risk. Given the rapid debilitating course of glioma, especially among the subset of older cases with the GBM histology, it is very difficult to uniformly collect self-reported histories. Our self-reported cases were younger and less likely to have a diagnosis of GBM. Although allergies were less common among these self-reported cases compared to controls, the relative case-control difference in symptoms was much more marked among proxy-reported cases. We cannot rule out that differential underreporting by proxies of cases' allergy histories might explain the much stronger observed associations among proxy-reported cases. Given the different age at onset and histology, the older proxy-reported cases might be etiologically distinct with respect to immunologic features. The descriptive epidemiology of both allergies and high-grade glioma have indicated a steady concomitant increase in incidence of both diseases,[24,25] which does not seem compatible with the observation that allergies would decrease risk of glioma. However, low-grade gliomas have been decreasing in incidence in the last 15 years,[24] and it is notable that allergy associations were strongest in non-GBM tumors, corresponding to the lower-grade gliomas, in both the self- and proxy-reported subgroups (Table VIII). Future studies will address any potential specificity among brain tumor histopathology and defined characteristics of allergy.

A lack of specificity between association of glioma with specific allergen and route of exposure provides some uncertainty regarding the possibility of an overall residual bias or confounding. We do not, however, believe that the allergy association in general is incorrect given our careful control of reported potential confounders, including age, gender, ethnicity and the large body of prior associations among cancer and reported allergies that is consistent with the association we observed here. Most meaningfully, significant results were found among self-reported cases *vs.* controls notably among combined respiratory allergens. In addition, we performed 1 analysis that strengthens the argument against significant reporting bias in the reporting of allergy history: We found that self- and proxy-reported cases showed similar rates of childhood allergies when adjusted by the decade cohort of birth (data not shown). Finally, a lack of specificity by allergen, symptom or route of exposure does not necessarily indicate a systematic bias in data collection but rather may reflect the complex pathology of allergy that can manifest differently in individuals given exposure and lifestyle characteristics.

Attempts to provide evidence for a "dose-response" for allergy on brain cancer risk produced mixed but not necessarily incompatible results. First, we considered an allergen as a categorical variable, regardless of reported severity, route of exposure or other characteristic. A clear "dose-response" emerged among all cases ($p < 0.0001$ for linear trend) and self-reported cases only *vs.* controls ($p = 0.02$, Table V). Another measure of dose, allergy severity, yielded a different result. Contrary to a typical "dose-response" expectation, mild allergies were more strongly inversely associated with gliomas than moderate or severe allergies but the differences between categories of severity were consistent with chance (Table VII). One possibility is that individuals with multiple allergies regardless of severity are more likely to be classified correctly as allergic. Individuals misclassified as allergic may have an intolerance to one specific food or toxin, for instance, but such an intolerance could in some cases be severe. Further study is needed to determine the precise nature of allergies using concrete biomarkers.

Our current study explores the role of lifetime history of allergy on the risk of glioma. Close to 85% of all controls in our study reported allergies (Table III). The frequencies of symptoms to allergens that would lead to rhinitis (hay fever) include pollens and

TABLE VIII – FREQUENCIES AND CASE-CONTROL ODDS RATIOS (OR) FOR ANY REPORTED ALLERGY *VS.* NO ALLERGIES AND ANY *VS.* NO ALLERGIES GROUPED BY LIKELY ROUTES OF EXPOSURE STRATIFIED BY GLIOBLASTOMA STATUS AND PROXY/SELF-REPORTED STATUS: THE SAN FRANCISCO BAY AREA GLIOMA STUDY, 1997–1999

	Controls (n = 402)		Proxy-reported nonglioblastoma cases (n = 29)				Self-reported nonglioblastoma cases (n = 141)				Proxy-reported glioblastoma cases (n = 107)				Self-reported glioblastoma cases (n = 128)			
Average age ± SE	55.3 ± 0.8		61 ± 3.8				46 ± 1.1				66 ± 1.2				58 ± 1.1			
	%[1]	#[2]	%[1]	#[2]	OR[3]	95% CI	%[1]	#[2]	OR[3]	95% CI	%[1]	#[2]	OR[3]	95% CI	%[1]	#[2]	OR[3]	95% CI
Route																		
Any allergy	84.6	340	44.8	13	0.16	0.07–0.35	78.0	110	0.55	0.33–0.92	63.6	68	0.37	0.22–0.61	78.9	101	0.70	0.42–1.16
Respiratory[4]	55.0	221	20.7	6	0.23	0.09–0.58	45.4	64	0.56	0.37–0.85	37.4	40	0.59	0.37–0.93	50.0	64	0.85	0.57–1.27
Dermal[5]	50.5	203	20.7	6	0.29	0.11–0.73	45.4	64	0.83	0.56–1.25	24.3	26	0.31	0.19–0.52	43.0	55	0.71	0.47–1.07
Digestive[6]	21.1	85	3.5	1	0.13	0.02–0.98	15.6	22	0.65	0.38–1.11	9.4	10	0.40	0.20–0.82	14.8	19	0.67	0.39–1.16

[1]Percent reporting allergy history to specified symptoms.–[2]Number of subjects reporting allergy symptoms.–[3]Case-control odds ratios adjusted for age, gender and ethnicity (white/nonwhite).–[4]House dust, molds, pollens, cats, dogs and other animals.–[5]Poison oak, insect stings/bites, soap and cosmetics.–[6]Eggs, dairy, shellfish, wheat, nuts (including peanuts) and other foods.

molds that have been reported to occur in 23–46% of adult subjects (Table IV). These frequencies are quite similar to other cross-sectional reports that use biomarkers of allergies to estimate prevalence,[25] providing some measure of validity to our data. Allergy, while often thought of as a childhood disease, is quite common in adults and regularly originates *de novo* in adulthood.[27] Positive skin tests in childhood or young adulthood are highly predictive for future allergy, indicating that the allergy "phenotype" may be a lifelong attribute.[28] Because glioma latency periods have not been established and may be decades, a lifetime assessment of immune-system function by questionnaire instrument is necessary in conjunction with biomarkers assessed at the time of study ascertainment. Our analysis of childhood onset *vs.* adulthood onset allergy in relation to glioma did not demonstrate differences in association (data not shown), providing some suggestion that propensity to allergy (regardless of age) drives the association reported here, which could be partially explained by genetic or other constitutional factors.

An inverse association between allergy and brain cancer is not surprising given the intimate relationship between the immune and the central nervous systems, as well as the putative role of the immune system in tumor immunosurveillance. Our results in the current study are consistent with our previous report, demonstrating an apparent deficit of individuals with serologic reactivity to Varicella virus among brain tumor cases compared to controls.[7,8] Our current study, combined with our previous reports, suggests that immune factors may be protective for gliomas. We speculate that those individuals with a biased immune response consisting of a primarily humoral, specifically IgE- and IgG4-mediated immune response (characteristic of allergy) may be more capable of preventing nascent brain tumors. This immunologic bias, whether developed through environmental influences or genetic predisposition, may lead to a lifelong proclivity for hyperresponsiveness to antigens manifesting both as allergies to external antigens and effective tumor immunosurveillance in the brain. Current understanding of the immune response suggests that tumor immunity is most effected by cell-mediated events, orchestrated by a class of T cells that support cytotoxic mechanisms against the tumor (T-helper 1). The evidence of such an immune reaction is common in resected brain tumors, showing the presence of macrophages, CD8 T and natural killer cells and inflammatory mediators. Nonetheless, it has been proposed that this cell-mediated response is largely ineffectual because of the action of glioma-derived immunosuppressive factors. These factors, which include transforming growth factor β, IL-10 and prostaglandin E2, are released during advanced glioma to cause suppression of cell-mediated immunity in the whole organism.[10] Indeed the normal function of central nervous system immune reactions appear to be orchestrated as humoral (antibody-mediated) in nature rather than cell-mediated, in theory to minimize collateral damage to the tissue architecture of the central nervous system that might be wrought by the vigorous inflammatory nature of a cell-mediated assault.[29,30] The inherent proclivity of atopic individuals to respond to "foreign" antigen (which could be a tumor-derived antigen) with a heightened humoral, or T-helper type-2 response, may allow the mounting of an appropriate immune response against emerging brain tumors resulting in the observed decreased frequency of such individuals among the case group. It is intriguing in this context to note the apparent efficacy of T-helper 2 cytokines IL-4 and Il-13 in inducing antiglioma response in animal models.[31–33] IL-4 also induces recruitment of eosinophils and macrophages to tumor sites, inducing tumor cell death and formation of microlumina, or high endothelial venules, which allows further immune response against tumor-derived antigens.[34,35] The exact nature of what constitutes "protective" immune function against brain cancer and how this might be exploited for therapeutic and preventative measures warrant further study.

The limitations of our study include the lack of a concrete biomarker for allergy as well as a definition of the precise pathophysiology of the allergic reaction. Application of such biomarkers

could help prevent the misclassification imparted by reporting bias, especially on the uncertainty of comparing self- and proxy-reported interviews. Whilst most allergies/asthma can be assumed to represent atopic (IgE-mediated) reactions, many other conditions may be mistaken for allergy, including food intolerances and chronic respiratory ailments. Our overall allergy prevalence among controls of 84.6% is much higher than reported in allergy prevalence studies that assessed allergy by a skin-prick assay for reaction to specific allergens, which estimate allergy prevalence between 20–46%.[26] These studies, however, assess a limited number of specific allergens, primarily airborne, as well as ignoring allergies that would be caused by non-IgE mechanisms such as many food allergies.[36] Even greater quantitative precision could be garnered from a laboratory assay of allergy parameters, such as precise IgE levels and functional assays of T cells. Indeed IgE levels are distributed in a normal distribution in the population (when logarithmically transformed[37]), making a categorical assessment of allergy as expressed in this article less than ideal. To overcome some of these limitations, functional assays will play a major role in our future studies of the possible role of allergies in glioma risk.

REFERENCES

1. Bondy M, Wiencke J, Wrensch M, et al. Genetics of primary brain tumors: a review. J Neurooncol 1994;18:69–81.
2. Caggana M, Kilgallen J, Conroy JM, et al. Associations between Ercc2 polymorphisms and gliomas. Cancer Epidemiol Biomark Prev 2001;10:355–60.
3. Chen P, Wiencke J, Aldape K, et al. Association of an ERCC1 polymorphism with adult-onset glioma. Cancer Epidemiol Biomark Prev 2000;9:843–7.
4. Chen P, Aldape K, Wiencke JK, et al. Ethnicity delineates different genetic pathways in malignant glioma. Cancer Res 2001;61:3949–54.
5. Shah KV. Does SV40 infection contribute to the development of human cancers? Rev Med Virol 2000;10:31–43.
6. Del Valle L, Gordon J, Assimakopoulou M, et al. Detection of JC virus DNA sequences and expression of the viral regulatory protein T-antigen in tumors of the central nervous system. Cancer Res 2001; 61:4287–93.
7. Wrensch M, Weinberg A, Wiencke J, et al. Prevalence of antibodies to four herpes viruses among adults with glioma and controls. Am J Epidemiol 2001;154:161–5.
8. Wrensch M, Weinberg A, Wiencke J, et al. Does prior infection with varicella-zoster virus influence risk of adult glioma? Am J Epidemiol 1997;145:594–7.
9. Sawamura Y, de Tribolet N. Immunobiology of brain tumors and implications for immunotherapy. In: Kaye AH, Laws ER, eds. Brain tumors: an encyclopedic approach. New York: Churchill Livingstone, 1995. 113–24.
10. Dix AR, Brooks WH, Roszman TL, et al. Immune defects observed in patients with primary malignant brain tumors. J Neuroimmunol 1999; 100:216–32.
11. Zou JP, Morford LA, Chougnet C, et al. Human glioma-induced immunosuppression involves soluble factor(s) that alters monocyte cytokine profile and surface markers. J Immunol 1999;162:4882–92.
12. Manjula S, Aroor AR, Raja A, et al. Serum immunoglobulins in brain tumours. Acta Neurochir 1992;115:103–5.
13. Barker CF, Billingham RE. Immunologically privileged sites. Adv Immunol 1977;25:1–54.
14. Antel J, Birnbaum G, Hartung H-P. Clinical neuroimmunology. Malden, MA: Blackwell Science, 1998.
15. Nasca PC, Baptiste MS, MacCubbin PA, et al. An epidemiologic case-control study of central nervous system tumors in children and parental occupational exposures. Am J Epidemiol 1988;128:1256–65.
16. Vena JE, Bona JR, Byers TE, et al. Allergy-related diseases and cancer: an inverse association. Am J Epidemiol 1985;122:66–74.
17. Schlehofer B, Blettner M, Preston-Martin S, et al. Role of medical history in brain tumour development. Results from the international adult brain tumour study. Int J Cancer 1999;82:155–60.
18. Brenner A, Linet M, Inskip P. History of allergies and risk of brain tumors. Toronto: Congress of Epidemiology, 2001. Abstract, p S120.
19. Schlehofer B, Blettner M, Becker N, et al. Medical risk factors and the development of brain tumors. Cancer 1992;69:2541–7.
20. Percy C, Van Holten V, Muir CS, eds. International classification of disease for oncology, 2nd ed. Geneva: World Health Organization, 1990.
21. Wrensch M, Lee M, Miike R, et al. Familial and personal medical history of cancer and nervous system conditions among adults with glioma and controls. Am J Epidemiol 1997;145:581–93.
22. AS/STAT User's Guide, 6th ed. Cary, NC: SAS Institute, Inc., 1990.
23. Schwartz J, Gold D, Dockery DW, et al. Predictors of asthma and persistent wheeze in a national sample of children in the United States. Association with social class, perinatal events, and race. Am Rev Respir Dis 1990;142:555–62.
24. Legler JM, Ries LA, Smith MA, et al. Cancer surveillance series [corrected]: brain and other central nervous system cancers: recent trends in incidence and mortality. J Natl Cancer Inst 1999;91:1382–90.
25. Howarth PH. Is allergy increasing? Early life influences. Clin Exp Allergy 1998;28 (Suppl 6):2–7.
26. Burr ML. Epidemiology of clinical allergy. Introduction. Monogr Allergy 1993;31:1–8.
27. Settipane RJ, Hagy GW, Settipane GA. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. Allergy Proc 1994;15:21–5.
28. Peat JK, Toelle BG, Dermand J, et al. Serum IgE levels, atopy, and asthma in young adults: results from a longitudinal cohort study. Allergy 1996;51:804–10.
29. Harling-Berg CJ, Park TJ, Knopf PM. Role of the cervical lymphatics in the Th2-type hierarchy of CNS immune regulation. J Neuroimmunol 1999;101:111–27.
30. Knopf PM, Harling-Berg CJ, Cserr HF, et al. Antigen-dependent intrathecal antibody synthesis in the normal rat brain: tissue entry and local retention of antigen-specific B cells. J Immunol 1998;161:692–701.
31. Benedetti S, Pirola B, Pollo B, et al. Gene therapy of experimental brain tumors using neural progenitor cells. Nat Med 2000;6:447–50.
32. Saleh M, Wiegmans A, Malone Q, et al. Effect of in situ retroviral interleukin-4 transfer on established intracranial tumors. J Natl Cancer Inst 1999;91:438–45.
33. Debinski W, Gibo DM, Hulet SW, et al. Receptor for interleukin 13 is a marker and therapeutic target for human high-grade gliomas. Clin Cancer Res 1999;5:985–90.
34. Kawano N, Ohba Y, Nagashima K. Eosinophilic inclusions in ependymoma represent microlumina: a light and electron microscopic study. Acta Neuropathol (Berl) 2000;99:214–8.
35. Tepper RI, Coffman RL, Leder P. An eosinophil-dependent mechanism for the antitumor effect of interleukin-4. Science 1992;257:548–51.
36. Bischoff SC, Mayer J, Wedemeyer J, et al. Colonoscopic allergen provocation (COLAP): a new diagnostic approach for gastrointestinal food allergy. Gut 1997;40:745–53.
37. Barbee RA, Halonen M, Lebowitz M, et al. Distribution of IgE in a community population sample: correlations with age, sex, and allergen skin test reactivity. J Allergy Clin Immunol 1981;68:106–11.