Increased rate of positive penicillin skin tests among patients with glioma: insights into the association between allergies and glioma risk

Clinical article

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Object. Allergy and immunoglobulin E levels are inversely associated with glioma risk. Previous studies have focused on respiratory and food allergies, and little information is available regarding drug allergies. This study evaluated the rate of positive penicillin skin tests (PenSTs) and blood eosinophil counts in a large population of patients with glioma compared with nontumor controls to provide evidence for the relationship between drug allergies and glioma risk.

Methods. A retrospective case-control study was conducted in patients diagnosed with glioma (n = 913) between January 2004 and June 2013. The study patients were matched with nontumor controls (n = 1091) for age, sex, and date of admission to the hospital. Preoperative results of the PenST and eosinophil counts were obtained, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using conditional logistic regression models, while a Kaplan-Meier analysis was used to assess overall survival.

Results. The percentage of positive PenSTs was higher among patients with glioma than in control subjects. The age-, sex-, and admission date–adjusted OR for positive versus negative PenSTs was 2.392 (95% CI 1.891–3.026). Eosinophil counts were also higher in glioma cases than in controls: the OR for eosinophil > 0.06 × 10^9/L versus ≤ 0.06 × 10^9/L was 1.923 (95% CI 1.608–2.301). There was no association between positive PenST/eosinophil counts and glioma grade or patient survival (n = 105).

Conclusions. In contrast to previously reported relationships between allergy and glioma, in the present study a significantly higher rate of positive PenSTs and higher eosinophil counts were found in patients with glioma than in nontumor controls. These results suggest a complex relationship between allergies and glioma development.

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Key Words • glioma • penicillin • allergy • eosinophil • skin test • case control • oncology

Abbreviations used in this paper: AVM = arteriovenous malformation; CI = confidence interval; OR = odds ratio; PenST = penicillin skin test.

Gliomas are the most common form of primary brain tumor and represent a significant health concern, especially as little is known about the etiology of glioma and no methods of prevention or cure are currently available. Glioma formation and progression are promoted by a microenvironment that confers immune privilege and tolerance, and ineffectual innate and adaptive immune responses are typically observed in patients with glioma. Thus, the occurrence of glioma is closely associated with immunological dysfunction.

Allergies represent a type of immunological disorder in which a decreased immune tolerance triggers an aberrant reaction to certain substances. Previous reports have indicated an inverse relationship between self-reported allergies or serum immunoglobulin E levels and glioma risk. Moreover, eosinophils, one of the major effector cell types of the immune system, have been implicated in allergies as well as gliomas. Although it is unclear whether the hypersensitivity associated with allergies predisposes against the development of gliomas, or if glioma occurrence inhibits allergies by immunosuppression, a lower incidence of allergies should nonetheless be observed among patients with glioma based on the published data. However, the term allergy describes a broad spectrum of pathologies, with symptoms and mechanisms that vary depending on the allergen. Moreover, ethnic differences in the prevalence and manifestation of allergies and related diseases have been reported. Earlier studies examining the association between allergies and gliomas mostly focused on respiratory and food allergies.
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in European and American Caucasian patients; as such, information on other types of allergies in other patient populations is needed. Unlike allergies such as asthma that can be provoked by a variety of factors, allergic reactions to drugs have a well-defined mechanism, which is useful for evaluating disease associations.

Allergy to the drug penicillin is common and can be diagnosed by a skin test (penicillin skin test [PenST]) that is routinely performed before surgery at our hospital to determine appropriate intra- and postoperative antibiotic prescription. Blood eosinophil counts can be obtained from the routine analysis of blood samples at the time of admission to the hospital. In this retrospective case-control study, the percentage of positive PenSTs and blood eosinophil counts in glioma patients and nontumor controls was investigated, and the relationship between penicillin allergy and glioma risk was analyzed.

Methods

Study Population

Consecutive patients diagnosed with glioma (n = 913) who underwent resection between January 2004 and June 2013 at the First Hospital of China Medical University were selected as the case population. Histological diagnoses were made according to the 2007 WHO classification guidelines by at least 2 neuropathologists from the Department of Pathology of China Medical University. The patient cohort consisted of 48 Grade I, 88 Grade II, 129 Grade III, and 648 Grade IV glioma cases.

Control subjects (n = 1091) were randomly selected from general patient lists by a preset algorithm, and were patients who had not been diagnosed with a brain tumor and were residents of the same region and within the same age range as the cases. Controls and case patients were matched in terms of sex and date of admission to the hospital. The cohort included 592 patients with aneurysms, 342 with brain injuries, 54 with Chiari malformations, and 121 with arteriovenous malformations (AVMs).

Clinicopathological data were retrospectively collected from medical records of cases and controls, including skin test results and blood eosinophil counts at the time of admission. Overall survival information was available for 105 Grade IV (glioblastoma) cases (11.5%), and was used in the survival analysis.

Penicillin Skin Test

The PenST (Minsheng Pharmaceutical Co.) consisting of an intracutaneous test performed on the day before surgery or upon emergency room admission, according to the manufacturer’s protocol. Briefly, 2500 units of penicillin were dissolved in 5 ml 0.9% NaCl. The intracutaneous test was performed on the volar forearm using 0.1 ml of the solution and was read after 20 minutes. Histamine (0.1 mg/ml) and isotonic NaCl were used as controls. Positive results, consisting of a wheal ≥ 1 cm in diameter surrounded by flare, were determined and recorded by at least 2 nurses. Prior to the PenST and blood examination, patients received no medications besides mannitol and dexamethasone. In total, 185 glioma cases, but no control subjects, received dexamethasone.

Blood Examination

Blood samples were collected in the morning after an overnight fast before medical intervention and were tested by staff at the Department of Clinical Laboratory within 2 hours of collection, using a Sysmex XE-2100 complete blood count analyzer. The analysis included blood eosinophil counts.

Statistical Analysis

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using conditional logistic regression to determine the association between PenST results and blood eosinophil counts and glioma risk, adjusted for age, sex, and date of admission. Eosinophil count was represented as a categorical variable with a cutoff value defining 2 categories, as described in the results. The date of admission was divided into two 5-year intervals (2004–2008 and 2009–2013). Age was classified as < 45 years, 45–59 years, or ≥ 60 years. Kaplan-Meier survival curves were generated to determine the distribution of overall survival according to PenST results or eosinophil counts, and were analyzed using the log-rank test. The chi-square test, Student t-test, and ANOVA were used to evaluate differences between groups. Analyses were performed using SPSS (version 19.0, IBM Corp.), and a 2-tailed p value < 0.05 was considered statistically significant.

Results

Characteristics of Study Patients

The study area was Northeast China, and all study patients and controls were Asian. Glioma case subjects and control subjects were matched with respect to age, sex, and time of admission (Table 1). Ages ranged from 9 to 80 years (mean 45.3 years) and 11 to 80 years (mean 44.7 years) for cases and controls, respectively. The male to female ratios were 57.2% to 42.8% for glioma patients and 56.7% to 43.3% for controls. For both admission date intervals, each case was matched to 1 or more controls.

Association Between Positive PenST Results and Glioma Incidence

The percentage of positive PenSTs was higher in glioma cases than in controls (25.2% vs 12.5%, p < 0.001; Fig. 1A). The case-control OR was 2.392 (95% CI 1.891–3.026; Table 2), even after adjustments were made for age, sex, and date of admission. Subsequent stratified analyses according to histological type, age, sex, and date of admission revealed that positive PenSTs were uniformly higher in cases than in controls in all subgroups (Fig. 2 upper).

The incidence of positive PenSTs did not vary with age or date of admission for cases or controls; in the glioma group, the incidence was similar for different glioma grades (Grade I, 27.1%; Grade II, 21.6%; Grade III, 24.8%; and Grade IV, 25.6%; p = 0.857; Fig. 1B). In total, 185 glioma cases received dexamethasone prior to the PenST. However, the incidence of positive PenSTs was similar for glioma patients with and without dexamethasone use.
TABLE 1: Description of glioma cases and controls

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Gioma Cases</th>
<th></th>
<th></th>
<th>Controls</th>
<th></th>
<th></th>
<th>p Value†</th>
<th>p Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Positive*</td>
<td>Negative*</td>
<td>All</td>
<td>Positive*</td>
<td>Negative*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>913</td>
<td>230 (25.2)</td>
<td>683 (74.8)</td>
<td>1091</td>
<td>136 (12.5)</td>
<td>955 (87.5)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age (yrs)</td>
<td>45.3</td>
<td>44.5</td>
<td>45.6</td>
<td>44.7</td>
<td>44.8</td>
<td>43.8</td>
<td>0.328</td>
<td>0.578</td>
</tr>
<tr>
<td>mean</td>
<td>14.1</td>
<td>13.6</td>
<td>14.3</td>
<td>19.9</td>
<td>20.1</td>
<td>19.1</td>
<td>0.000</td>
<td>0.844</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sex (%)</td>
<td>male</td>
<td>522 (57.2)</td>
<td>118 (22.6)</td>
<td>404 (77.4)</td>
<td>619 (56.7)</td>
<td>61 (9.9)</td>
<td>0.038</td>
<td>0.003</td>
</tr>
<tr>
<td>sex (%)</td>
<td>female</td>
<td>391 (42.8)</td>
<td>112 (28.6)</td>
<td>279 (71.4)</td>
<td>472 (43.3)</td>
<td>75 (15.9)</td>
<td>0.019</td>
<td>0.003</td>
</tr>
<tr>
<td>time period (%)</td>
<td>2009–2013</td>
<td>532 (58.3)</td>
<td>129 (24.2)</td>
<td>403 (75.8)</td>
<td>697 (63.9)</td>
<td>94 (13.5)</td>
<td>0.438</td>
<td>0.017</td>
</tr>
<tr>
<td>time period (%)</td>
<td>2004–2008</td>
<td>381 (41.7)</td>
<td>101 (26.5)</td>
<td>280 (73.5)</td>
<td>394 (36.1)</td>
<td>42 (10.7)</td>
<td>0.438</td>
<td>0.017</td>
</tr>
<tr>
<td>eosinophil level</td>
<td>mean</td>
<td>0.12</td>
<td>0.12</td>
<td>0.11</td>
<td>0.12</td>
<td>0.12</td>
<td>0.932</td>
<td>0.107</td>
</tr>
<tr>
<td>eosinophil level</td>
<td>SD</td>
<td>0.14</td>
<td>0.15</td>
<td>0.14</td>
<td>0.16</td>
<td>0.15</td>
<td>0.14</td>
<td>0.16</td>
</tr>
<tr>
<td>dexamethasone (%)</td>
<td>used</td>
<td>185 (20.3)</td>
<td>49 (26.5)</td>
<td>136 (73.5)</td>
<td>547 (75.1)</td>
<td></td>
<td>0.650</td>
<td></td>
</tr>
<tr>
<td>dexamethasone (%)</td>
<td>not used</td>
<td>728 (79.7)</td>
<td>181 (24.9)</td>
<td>547 (57.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>glioma Grade (%)</td>
<td>I</td>
<td>48 (5.3)</td>
<td>13 (27.1)</td>
<td>35 (72.9)</td>
<td></td>
<td></td>
<td>0.857</td>
<td></td>
</tr>
<tr>
<td>glioma Grade (%)</td>
<td>II</td>
<td>88 (9.6)</td>
<td>19 (21.6)</td>
<td>69 (78.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>glioma Grade (%)</td>
<td>III</td>
<td>129 (14.1)</td>
<td>32 (24.8)</td>
<td>97 (75.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>glioma Grade (%)</td>
<td>IV</td>
<td>648 (71.0)</td>
<td>166 (25.6)</td>
<td>482 (74.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>controls (%)</td>
<td>aneurysm</td>
<td></td>
<td></td>
<td>592 (54.3)</td>
<td>68 (11.5)</td>
<td></td>
<td>0.107</td>
<td></td>
</tr>
<tr>
<td>controls (%)</td>
<td>brain injury</td>
<td></td>
<td></td>
<td>324 (29.7)</td>
<td>52 (16.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>controls (%)</td>
<td>Chiari malformation</td>
<td>54 (4.9)</td>
<td>5 (9.3)</td>
<td></td>
<td>49 (90.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>controls (%)</td>
<td>AVM</td>
<td>121 (11.1)</td>
<td>11 (9.1)</td>
<td>110 (90.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Penicillin skin test positive/negative.
† Penicillin skin test positive versus penicillin skin test negative. Boldface type indicates statistical significance at p value < 0.05.
‡ Cases versus controls.
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(26.5% vs 24.9%, \( p = 0.650 \), Table 1). Moreover, in the control group, the rate of positive PenSTs was similar for patients with aneurysms (11.5%), brain injuries (16.0%), Chiari malformations (9.3%), and AVMs (9.1%; \( p = 0.107 \); Fig. 1B). Among both the cases and the controls, positive PenSTs were more frequently observed among females than males (Table 1), consistent with what has been previously reported.\(^{23}\)

Prior to the PenST, seizures were found in 319 glioma cases (34.9%) and 278 control subjects (25.5%). For glioma cases, the incidence of positive PenSTs was 23.8% (76/319) in patients with seizure and 25.9% (154/594) in patients without seizure (\( p = 0.486 \)). For control subjects, the incidence of positive PenSTs was 10.1% (28/278) in patients with seizure and 13.3% (108/813) in patients without seizure (\( p = 0.162 \)). Prior to the PenST, enhanced MRI was performed in 812 glioma cases (88.9%) and 196 control subjects (18%). For glioma cases, the incidence of positive PenSTs was 25.7% (209/812) in patients who underwent enhanced MRI and 20.8% (21/101) in patients who did not (\( p = 0.280 \)). For control subjects, the incidence of positive PenSTs was 12.2% (24/196) in patients who underwent enhanced MRI and 12.5% (112/895) in patients who did not (\( p = 0.918 \)). Thus, the incidence of positive PenSTs did not vary with seizure or contrast agents.

**Fig. 1.** Penicillin skin test (PenST) results and blood eosinophil counts (\( \times 10^9/L \)) in glioma cases and control subjects. The percentage of positive PenSTs (A) and eosinophil counts (C) were significantly higher in cases than in controls. The percentages of positive PenSTs (B) and eosinophil counts (D) in glioma Grades I–IV (cases), and aneurysms, brain injuries, Chiari malformations, and AVMs (controls) were not significantly different.

**TABLE 2: Multivariate ORs for PenSTs and eosinophil levels for each group**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Glioma Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
<th>p Value</th>
<th>Glioblastoma Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PenST negative</td>
<td>683</td>
<td>955</td>
<td>1</td>
<td>&lt;0.001</td>
<td>482</td>
<td>701</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>positive</td>
<td>230</td>
<td>136</td>
<td>2.392 (1.891–3.026)</td>
<td>&lt;0.001</td>
<td>166</td>
<td>97</td>
<td>2.508 (1.901–3.309)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eosinophil levels (( \times 10^9/L )) ≤0.06</td>
<td>403</td>
<td>656</td>
<td>1</td>
<td>&lt;0.001</td>
<td>294</td>
<td>493</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>510</td>
<td>435</td>
<td>1.923 (1.608–2.301)</td>
<td>&lt;0.001</td>
<td>354</td>
<td>305</td>
<td>1.949 (1.578–2.409)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\* Odds ratios were adjusted for sex, age, and admission date.
controls (mean $0.12 \times 10^9/L$ vs $0.08 \times 10^9/L$; $p < 0.001$; Table 1, Fig. 1C). Because the median eosinophil count of the 2004 total individuals in this study (913 glioma cases and 1091 controls) was $0.06 \times 10^9/L$, this value was defined as the cutoff to distinguish high from low eosinophil counts. The case-control OR for the counts was 1.923 (95% CI 1.608–2.301; Table 2) adjusted for age, sex, and date of admission. Stratified analyses according to histological type, age, sex, and date of admission showed counts that were consistently higher in cases than in controls (Fig. 2 lower).

We used all 2004 individuals in the study to construct the receiver-operating characteristic curve to evaluate the predictive performance of the eosinophil counts for patients with glioma. Based on the receiver-operating characteristic curve, we found that at the median eosinophil count ($0.06 \times 10^9/L$) the discriminative power was 58% specificity and 60% sensitivity (Fig. 3).

Eosinophil counts were not correlated with PenST results in either cases or controls (Table 1), consistent with the low concordance between immunoglobulin E levels and self-reported allergies that has been observed. In total, 185 glioma cases received dexamethasone prior to the blood examination. However, the eosinophil counts were similar for glioma patients with or without dexamethasone use ($0.111 \times 10^9/L$ vs $0.115 \times 10^9/L$, $p = 0.678$). In the glioma group, there were no significant differences in eosinophil counts among glioma grades, and in the control group, counts were similar among all subjects (Fig. 1D).

For glioma cases, the average eosinophil counts were $0.126 \times 10^9/L$ in patients with seizure and $0.111 \times 10^9/L$ in patients without seizure ($p = 0.151$). For control subjects, the average eosinophil counts were $0.085 \times 10^9/L$ in patients with seizure and $0.087 \times 10^9/L$ in patients without seizure ($p = 0.901$). For glioma cases, the average eosinophil counts were $0.115 \times 10^9/L$ in patients who underwent...
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![Graph](image)

**Fig. 3.** Receiver-operating characteristic curve analysis of eosinophil counts. In the 2004 total individuals in the study, at the median level (0.06 × 10^9/L) of eosinophil counts, the discriminative power was 60% sensitivity and 58% specificity for glioma cases compared with nontumor controls. AUC = area under the curve.

enhanced MRI and 0.125 × 10^9/L in patients who did not (p = 0.534). For control subjects, the average eosinophil counts were 0.082 × 10^9/L in patients who underwent enhanced MRI and 0.087 × 10^9/L in patients who did not (p = 0.673). Thus, the eosinophil counts also did not vary with seizure or contrast agent.

**Prognostic Value of Positive PenSTs and Eosinophil Counts**

Overall survival information was available for 105 Grade IV (glioblastoma) cases, including 62 males (59.0%) and 43 females (41.0%), with ages ranging from 19 to 76 years (mean 52.4 ± 13.4 years). All patients underwent resection between 2009 and 2013. Among these patients, 24 (22.9%) showed positive PenST results, while 81 cases (77.1%) were negative. Low eosinophil counts were observed in 54 cases, with 51 cases showing high counts. The Kaplan-Meier survival curve indicated that neither PenST results nor blood eosinophil counts was significantly correlated with survival in patients with glioblastoma (Fig. 4), or associated with the overall survival of patients, as determined by the Cox regression analysis.

**Discussion**

Glioma risk has been shown to be inversely associated with a history of allergy and allergy-associated immunoglobulin E levels, which indicates that a lower occurrence of allergies should be observed among patients with glioma. Eosinophils are major effectors in immune responses, including allergic reactions, and an association between eosinophils and glioma has been suggested. Thus, in the present study we examined the rate of penicillin allergy and the eosinophil counts in a large series of patients with glioma in comparison with nontumor controls. At our hospital, the PenST is routinely administered in preparation for neurosurgery, and eosinophil counts were obtained from preoperative blood tests; thus, unlike in previous questionnaire-based studies, available medical records and the results of clinical examinations were used to assess patient risk and outcomes. Unexpectedly, the analyses showed that the rate of positive PenSTs, as well as eosinophil counts, was higher in glioma cases than in controls (Figs. 1 and 2). Two different interpretations of these results are presented below.

The occurrence of glioma may increase the probability of testing positive for allergy to penicillin, and may also lead to elevated eosinophil counts. However, this possibility is unlikely, given that immune function is compromised in patients with glioma, which is manifested by cutaneous anergy to common bacterial antigens, lymphopenia, and an inability to mount delayed-type hypersensitivity responses to common recall antigens or neoantigens in vivo. Glioma patients also exhibit decreased antibody response and impaired T-cell cytotoxicity. These immunological defects are at odds with a heightened sensitivity to penicillin. Nevertheless, it is unclear from which time point a tumor exerts immunological suppression, and whether the PenST was performed before or after that point. Moreover, it is not known whether other types of immune disorders such as hypersensitivity can also be triggered by gliomas; thus, the possibility that gliomas can increase positive PenSTs and eosinophil counts cannot be discounted, although no tumor-induced hypersensitivity has been found in any other kind of tumor.

Alternatively, a positive PenST result may be a risk factor for gliomas. Interestingly, the percentage of positive PenSTs was still higher in patients with low-grade (Grade I and II) gliomas whose immune function should not have been significantly disturbed. No correlation was observed between a positive result and tumor grade or prognosis (Figs. 1 and 4), suggesting that an allergy to penicillin may be implicated in glioma development rather than progression. It has been reported that allergies are immune abnormalities that increase disease susceptibility under certain circumstances. For example, asthma patients are vulnerable to viral respiratory infections, particularly human rhinovirus, and eosinophils are often detected in asthmatic airways. The occurrence of atopic dermatitis, an immune-related disorder, increased the risk of brain tumor and other cancers. In this study, the rate of positive PenST and blood eosinophil counts was higher in glioma cases than in controls (Fig. 2), indicating that the presence of eosinophils, and a heightened penicillin allergic response, may be related to high glioma susceptibility.

The present findings that high positive PenST results exist in patients with glioma are in contrast to earlier reports of an inverse association between self-reported allergies and glioma risk. This discrepancy could be due to several reasons. First, drug allergies differ from respiratory and food allergies in terms of the physiological changes that are induced. For instance, it has been shown that penicillin allergies, which are often delayed reactions, involve an immunoglobulin E–independent mechanism, while respiratory allergies such as asthma occur instantaneously as a result of immunoglobulin E–mediated hypersensitivity. Second, respiratory and food allergies are typically manifested during routine daily activities, while a drug allergy is less apparent, and
is often only identified by clinical examination or treatment. Third, unlike allergic diseases (e.g., asthma and eczema) that have complex origins, drug allergies are mechanistically straightforward. And fourth, ethnic differences among patient cohorts in the various studies may have also contributed to the conflicting findings. Previous studies examined European and American (Caucasian) subjects, while the subjects in the present study were Asian. Allergic diseases have different epidemiological and clinical manifestations, and may involve different genetic and epigenetic mechanisms depending on ethnicity, which may in turn be associated with variable glioma risk.

Eosinophil counts were found to be higher in cases than controls, while the values were within normal ranges. Moreover, blood eosinophil counts and immunoglobulin E levels are dynamic. All these factors may affect the results analysis. However, we believe that the observed results may be clinically meaningful. Eosinophils produce eosinophil peroxidase and reactive oxygen species upon activation by the cytokine granulocyte-macrophage colony-stimulating factor, which may amplify oxidative damage and promote tumorigenesis in the lungs. Human astrocytes and glioblastoma cells also produce granulocyte-macrophage colony-stimulating factor, and the resultant oxidative stress may contribute to tumor malignancy. Additional studies are required to more closely examine the causal relationship between tumor-infiltrating eosinophils and glioma development and progression. Moreover, the value of the eosinophil counts in predicting patients with glioma also requires validation in future studies.

There are several limitations to the present study. Selection bias is possible in this single-center retrospective trial, and chance findings may be generated. To reduce selection bias, all patients with glioma at the hospital during the study period (January 2004 to June 2013) were included in the analyses, without additional selection. The control cohort consisted of hospital patients rather than normal, healthy subjects. However, for comparative analysis of penicillin allergy, control subjects should be tested using penicillin with the same lot number during the same period of time as the experimental group. For this retrospective study, no normal subjects met the above criteria. All the control subjects were matched with the case subjects based on sex, age, and time of admission. Thus, the control subjects in this study were the best available to us. The results showed that positive PenSTs were observed at similar frequencies among the 4 subsets of control subjects, and collectively, the incidence of positive results (12.5%) was comparable to what has been observed in the general population (7.3%–10.2%). All of these results indicated that the control subjects might be able to represent normal subjects. Although no significant differences were observed in eosinophil counts and PenST results between glioma patients with or without steroid use, steroids may have confounded the results. Other factors such as contrast agent or seizure may also confound this observation, although they cannot explain the findings of the present study. Finally, given the limitations of the research, this study was unable to establish a causal relationship between penicillin allergy and glioma risk.

Conclusions

The findings of the present study demonstrate that positive PenSTs and high eosinophil counts are correlated with glioma, which is contrary to previous results regarding allergy and glioma. These results point to a complex relationship between allergic reactions and glioma inci-
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dence, which may be affected by multiple factors. How-
ever, confounding factors and bias need to be considered. Additional studies are required to gain insight into the interdependence of allergic pathology and the development of brain malignancies.

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Disclosure

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