

Allergies and Adult Gliomas: Cohort Results Strengthen Evidence for a Causal Association

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The evidence for an association between a history of allergies and a reduced risk of glioma has been emerging (1). In this issue of the Journal, Calboli et al. (2) analyze associations between prediagnostic plasma immunoglobulin E (IgE) levels and the risk of adult glioma by combining data from four large prospective cohort studies. The pooled data resulted in a modest number of 169 glioma cases, but for a rare disease, this is a substantial contribution to the literature. A statistically significant protective association with borderline elevated levels of total IgE (25–100 kU/L) relative to clinically normal levels (<25 kU/L) was observed in men and women, but an association with elevated levels of total IgE (>100 kU/L) was not observed. The findings are somewhat perplexing, but further our understanding of the biological underpinnings of the protection that allergies appear to provide in the development of brain tumors.

The results of Calboli et al. (2) are consistent with one other cohort study that reported a statistically significant inverse association between risk of glioma and borderline elevated levels of IgE, but inconsistent associations with elevated IgE levels (3). This study (2) estimated an odds ratio (OR) near unity at elevated total IgE levels, whereas Schlehofer et al. (3) reported a protective association with elevated levels of respiratory allergen-specific IgE. They observed that the higher the level of respiratory allergen-specific IgE, the stronger was the association, and an increased association was statistically significant in patients with high grade glioma (3). Together, these studies point to an association between prediagnosis IgE level and risk of glioma, but the biological mechanism underlying this association is still unclear.

The suggestion that allergies may be associated with a reduced risk of developing of brain tumors was made in the early 1990s (4). Since then, 10 case-control and two cohort studies have investigated this association using self-reported data on the history of allergic conditions. Results showed an inverse association of glioma risk with any allergic conditions compared with nonallergic conditions (pooled estimated OR = 0.60, 95% confidence interval [CI] = 0.52 to 0.69) (1). The association was statistically significant when limited to asthma, eczema, and hay fever as a group, and the association remained when consideration of proxy reporting was introduced in the analysis (1). These estimates based on self-report of allergies are similar to that observed by Calboli et al. (2) (total IgE 25–100 vs <25 kU/L, OR = 0.63, 95% CI = 0.42 to 0.93).

Evidence of association between allergy and glioma has accumulated to the point that it is worth taking a moment to evaluate if this repeated observation meets causal criteria used in population

studies, such as temporality, magnitude of the association, dose-response, consistency, and biological plausibility. The temporality of allergy can be questioned in case-control studies, which are based on self-report of a history of allergies after a diagnosis of brain tumors has been made, but the timing of the allergies and development of the gliomas have now been well characterized in two cohort studies (3,5), in addition to the Calboli et al study (2). The magnitude of the association observed in humans is also substantial. Two meta-analyses have reported summary odds ratio estimates reflecting an inverse relationship between self-reported allergic disease and glioma (1,6); the most recent showing a 40% decreased risk of glioma (1).

Although case-control studies provide an indirect measure of dose-response, it was observed that the number of types of allergies a person reports is inversely associated with glioma risk (7,8). Most studies do report an inverse association, although inconsistencies by type of allergy are present, and these may be a result of inconsistencies in the definition of allergic disease used in data collection. Asthma and allergies are constellations of diseases with distinct genetic and environmental effects but also gene-environment interactions. Investigators usually measure allergic diseases by self-report, IgE levels (total and/or allergen specific), and single-nucleotide polymorphisms associated with asthma and allergic diseases. All these methods have their limitations. Self-report might be affected by recall bias, and IgE levels might be affected by the presence of disease, and although single-nucleotide polymorphisms might not be affected by recall bias or the presence of disease, there is no conclusive evidence that they are related to the allergic phenotype. Studies have demonstrated that glioma patients have impairments in both the humoral and cellular immune system that are associated with the grade of glioma (9,10), but these observations could be a result of reverse causality. One observation that appears to be emerging is that this association may vary by tumor subtype, histology, or tumor aggressiveness [Calboli et al. (2) and Scheurer et al. (11)].

Given the strength of the emerging evidence for an association between allergies and glioma, the current challenge is to understand the biological plausibility of this observation. The initial focus has logically been on immune regulation in the central nervous system leading to increased immunosurveillance (12). The problem is that higher IgE levels do not necessarily correlate with increased immunosurveillance. Although IgE is extensively studied and well understood in allergic diseases (13), the role of IgE in gliomas, as well as other cancers, is paradoxical and might be site specific (14).

Measuring prediagnosis IgE levels from cohorts is the best way to study this association. Studies by Calboli et al. (2) and Schlehofer et al. (3) are the only ones to date to study the association between prediagnosis IgE level and glioma. Whereas Calboli et al. (2) measured total, respiratory allergen-specific, and food allergen-specific IgE, Schlehofer et al. (3) only measured respiratory allergen-specific IgE. Both studies were able to demonstrate an association between IgE levels and glioma risk, but subgroup analysis reduced the statistical power and produced confidence intervals that included 1. Unlike Schlehofer et al. (3), Calboli et al. (2) and Wiemels et al. (15) (using a case-control study design) observed an association between borderline elevated levels of total IgE and glioma when compared with clinically normal IgE levels, but the association was not apparent at elevated IgE levels. Concern has been raised that the drug temozolomide which lowers total IgE levels, may have confounded the relationship reported in a case-control study (15); a bias that can be ruled out in the current pooled cohort study (2), because it has the strong advantage of having prediagnostic measures of IgE.

A larger sample size is needed to see if this association with borderline levels of IgE can be replicated. If so, it could mean that the levels of IgE required to elicit an allergic response might be different than the levels needed to protect against glioma development. The next step may be to conduct a pooled analysis of reported cohorts to examine the association between prediagnostic IgE and glioma risk in greater detail, providing increased statistical power for subgroup and trend analyses. In addition, case-control studies conducted to better explore the dose-response issues in terms of number and timing of allergies may be helpful in demonstrating consistency between self-report and allergen-specific IgE results.

In summary, the association between allergy and glioma fulfills the major causal criteria—temporality (cohort studies), strength of the association (similar estimates from case-control, cohort, and pooled analysis studies), dose-response (self-report case-control studies), consistency (most studies are in the same direction), and biological plausibility (increased immune response). The weaker links are the potential misclassification of exposure (allergic diseases), limited evidence for dose-response effects, and the small sample size of glioma cases. The study by Calboli et al. (2) strengthens the evidence of this association by providing a prediagnostic measure of allergen sensitivity in a large cohort that allows a relatively robust estimate of association for this uncommon tumor.

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Funding

National Center on Minority Health and Health Disparities (grant number 1 P60 MD003424-01 to UAA).

Notes

The authors declare no conflict of interest.

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