

Research Reinforces Potential Allergies-Glioma Connection

By Mike Martin

Research reported in 2011 from several American and European universities supports the decades-old hypothesis that people with allergies have a low incidence of glioma: up to four times lower than that of non-allergy sufferers in some studies.

First identified two decades ago, the inverse relationship between allergies and glioma “is one of the most consistent associations in the brain tumor literature,” wrote Darrell Bigner, M.D., Ph.D., director of the Duke University Tisch Brain Tumor Center, in a February 2011 *Cancer Epidemiology* paper.

Although past studies have failed to confirm the inverse allergy association in meningioma and acoustic neuroma, they have confirmed it for glial cells.

The most recent study, published in the Oct. 18 *JNCI*, found a statistically significant inverse association between glioma and borderline-elevated total immunoglobulin E (IgE), a biomarker often found in allergy sufferers. Healthy participants from four cohorts contributed blood samples well before brain tumors developed, suggesting that any chemotherapy- or tumor-induced immune alterations “were unlikely to cause the observed changes in IgE,”

explained study coauthor and Brown University epidemiology professor Dominique Michaud, Ph.D.

The findings were consistent with those of case-control studies, Michaud wrote with Imperial College School of Public Health researcher Federico Calboli, Ph.D., along with a team from Harvard Medical School.

According to Michael Schulder, M.D., vice chairman of neurosurgery at North Shore University Hospital in Manhasset, N.Y., although the observed inverse allergy-glioma relationship is not yet clinically relevant, “it may represent a serendipitous

observation that could unlock a lot of important clinical science.”

Solving a Mystery

Clinical relevance is most likely to emerge, experts say, from the mechanism by which allergies reduce glioma incidence if the inverse association is indeed causal, a mystery that virtually every study touches on. The idea that the same hypervigilant immune surveillance that causes allergies may also quash tumor cells is the leading contender among suggested mechanisms. But that idea falls short, experts say, mainly because the blood-brain barrier renders immune mechanisms not altogether inactive but, rather, muted in the brain.

A better explanation may be the prophylaxis, or toxin, hypothesis, said Cornell University neurobiology professor Paul Sherman, Ph.D., who in a December 2008 *Quarterly Review of Biology* paper applied the concept to every study on allergies and cancer since 1953. Proposed by University of California, Berkeley, evolutionary biologist Margie Profet in a 1991 *Quarterly Review of Biology* paper, the prophylaxis hypothesis asserts that allergies evolved through Darwinian natural selection as a “last line of defense” against carcinogens and mutagens.

“The IgE system and associated allergy symptoms may serve a common protective mechanism: the rapid expulsion of pathogens, dangerous natural toxins, and carcinogenic antigens before they can trigger malignant neoplasm,” wrote Cornell University evolutionary biologist and team member Janet Shellman-Sherman, Ph.D., applying the prophylaxis argument to cancer. The Sherman study is the only study to date of any potential mechanisms behind the allergy-cancer relationship.

Allergy symptoms such as coughing, sneezing, and diarrhea physically expel carcinogens from the body, Profet argued. Biochemically, IgE antibodies “target the specific molecular configurations of muta-

gens and carcinogens that have evaded general defense mechanisms.”

Decreases in blood pressure that accompany anaphylactic shock, bronchial constriction, and swollen sinuses play a related role, Profet claimed, reducing or blocking an allergenic toxin’s ability to circulate.

Her paper even suggests that allergenicity is a measure of carcinogenicity. The four most carcinogenic metals—arsenic, beryllium, chromium, and nickel—are also the most allergenic, Profet notes, and allergens such as Birch pollen and Brazil nuts contain potent carcinogens such as caffeic acid, sesquiterpene lactones, and nickel.

The idea that allergenicity and carcinogenicity are related emerged after Profet and UC-Berkeley toxicologist Bruce Ames, Ph.D., used the Ames test—a measure of

carcinogenicity—to identify hundreds of naturally occurring carcinogens, many also allergenic. Some surprising examples include isothiocyanate in cabbage, 8-methoxysporalen in celery, and safrole in black pepper and

nutmeg. Aflatoxin in mold is an example of a carcinogen found as a contaminant in some foods. “Natural and synthetic chemicals are equally likely to be positive for carcinogenicity in animal cancer tests,” Ames concluded. And Profet wrote, “The possibility that allergy evolved to defend against toxins has been overlooked, and the toxicity of most allergens has not been appreciated.”

From Cases to Cohorts

A team led by Harvard Medical School associate neurology professor Fred Hochberg, M.D., first identified an inverse relationship between glioma and allergy. In a 1990 *Journal of Neuro-Oncology* study of 160 glioblastoma and astrocytoma patients, they examined allergies, family history of central nervous system malignancies, cranial irradiation, cigarette smoking, alcohol consumption, drug use, and intake of cured or smoked foods.

Comparing with 128 healthy control subjects, the researchers reported “evidence that glioblastoma is associated with a decreased susceptibility to allergies” but was unrelated to the other factors.

Papers followed from case-control studies in the U.S., Sweden, the UK, Germany, Norway, Finland, and Denmark with the same essential finding: “a significant inverse association between glioma and history of allergies,” as a seven-member team led by National Cancer Institute radiation epidemiologist Alina Brenner, Ph.D., reported in a 2002 *International Journal of Cancer* paper.

Typical of case-control approaches, a 2009 *International Journal of Cancer* study led by University of California, San Francisco, associate professor of cancer epidemiology Joseph Wiemels, Ph.D., asked



Margie Profet

subjects whether they “ever had reactions to dust, mold, pollens, shellfish, nuts, cats,” and other allergens. The questionnaire also asked which symptoms subjects experienced, from runny nose to anaphylactic shock.

To eliminate factors that might confound study results, Ohio State University epidemiology professor Judith Schwartzbaum, Ph.D., published the first allergy-glioma cohort study in the *International Journal of Cancer* in 2003. Cohort studies have since eliminated antihistamine use (diphenhydramine may be mildly carcinogenic); chemotherapy (temozolomide lowers total IgE levels); and so-called proxy reporting errors, study questions that family members incorrectly answer when patients have either died or become incapacitated.

The October *JNCI* study and a European study led by the German Cancer Research Center’s Schlehofer and published in a July 2011 issue of *Allergy* suggest that glioma’s potential for immune suppression is not confounding results either, Wiemels said. “These studies do a lot to confirm that this

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is a true observation not based on any sort of bias,” he explained.

Finally, several studies have shown that the inverse association is dose dependent. The risk of developing glioma decreased 31%–45% with each additional allergy, a team led by Duke University Comprehensive Cancer Center epidemiologist Dora Il'yasova, Ph.D., reported in

a 2009 *Cancer Epidemiology, Biomarkers, and Prevention* paper. If hay fever reduces glioma risk by half, for instance, hay fever plus cat dander allergy might reduce it by 60%; hay fever plus cat allergy plus an allergy to Brazil nuts by 80%; and so forth.

The biggest questions remain about the risk-reduction mechanism, which “is thought to be elimination of procancerous

cells by increased immunosurveillance,” Il'yasova reported.

Evolution, Revolution, or No Go?

The prophylaxis mechanism predicts that cancers of tissues most likely to interact with the external environment are more likely than other cancers to be inversely related to allergies, the Cornell team found.

Consistent with the findings of past research, these tissues include gray matter but exclude the meninges. Eight studies since 2002 have shown that ultrafine airborne particles, viruses, and drugs deposited on nasal mucosa rapidly traverse the blood–brain barrier via the olfactory nerve and nasal epithelium—except when sinuses are allergically swollen, Cornell’s Sherman explained.

People with severe allergies also have lower concentrations of environmental carcinogens in their blood, a finding consistent with the prophylaxis argument, Sherman said. A 2002 Belgian case–control study found high IgE levels statistically correlating with low dioxin-like hydrocarbons, and a 2006 Western Australia population study found inverse correlations between circulating allergy-associated cytokines and PCB (polychlorinated biphenyl), organochlorine pesticides, and dichloroethylene.

Despite the epidemiological evidence, Wiemels said he finds the prophylaxis hypothesis “interesting” but doesn’t see allergy’s evolutionary benefits.

The heightened immune-surveillance mechanism makes better sense to Michael Scholder. First recognized at the cellular level as “nonself” and rapidly destroyed by the immune system, a nascent glioma would never become clinically or pathologically

apparent, giving the appearance of allergy-related prevention, Scholder explained.

“Immunity–cancer discussions like this have been going on for decades,” he said. “Does an immune mechanism exist? Can it be stimulated? We still don’t know.”

The Allergist–Oncologist

With a global task force, annual symposium, and textbook coedited by University of Vienna pathophysiology professor Erika Jensen-Jarolim, M.D., and UCLA Geffen School of Medicine surgery and immunology professor Manuel Penichet, M.D., Ph.D., “allergo-oncology” is a burgeoning field, but without an as yet clear, clinical purpose.

To change that, allergo-oncology research needs to move into the laboratory, Ohio State’s Schwartzbaum said. “You can’t make inferences from observational studies alone,” she explained. “We still need laboratory work after the epidemiology results come in.”

Given glioma’s rare incidence, “we also need larger cohorts,” she added. “My cohort results and others are based on relatively small sample sizes.”

Long-term use of the newer drug omalizumab (Xolair), which blocks all IgE-mediated allergy symptoms, should offer new opportunities for more cohort studies, Sherman explained. “People who cannot

mount allergy symptoms should be more at risk for cancers such as glioma.”

Given the lack of other consistent relationships between environmental factors and glioma risk, Scholder hopes that continued population studies, both case–control and cohort, will encourage clinical research. “Epidemiology often leads to clinical relevance, a good example being the link between cancer and smoking,” he said.

In all, the need for larger cohorts, reproducible laboratory findings, and that important missing mechanism leave the allergy–glioma question unresolved, Brown’s Michaud explained. “Studies such as ours and others may point to new etiologies,” he said. “But we are far from understanding what causes glioma.”

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