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Has allergenic pollen an impact on non-allergic diseases?

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Summary
Recent observations suggest that pollen do not only interacts with the human immune system to elicit an allergic response in susceptible individuals. It would have a much broader impact on human health. This applies more especially, yet not exclusively, to three groups of diseases: non-allergic respiratory conditions, cardio- and cerebrovascular accidents, and psychiatric disorders including suicide and suicide attempt. At present, the reasons for these unexpected connections are only hypothetical, and require further exploration in larger samples, but there is perhaps a multitude of them. One must therefore favour a holistic approach of pollen and its impact on human health.

Introduction

Both clinical experience and scientific literature indicate airborne pollen as an important trigger of allergic symptoms, namely allergic respiratory diseases – especially hay fever and asthma –, allergic eye irritations and to a lesser extent allergic skin diseases. However, some observations have been published in the last decade, suggesting as well an effect of allergenic pollen on several non-allergic diseases (1). These studies have generally analyzed the relationship between daily variations in pollen counts and daily variations in health effects quantified at population levels (time-series), for instance through hospital or emergency room admissions or, more rarely, through mortality. Despite some limitations, including the difficulty in moving from an observed association to a causal inference, these findings already deserve to be discussed.

The aim of the present paper is therefore to provide a review of papers published since 1999 in peer reviewed journals to support the theory that links allergenic pollen and various other-than-allergic diseases. Non-allergic respiratory conditions, cardio- and cerebrovascular accidents, and psychiatric disorders are successively considered before a general discussion that refers also to a few other pathologic relationships.

Effects on non-allergic respiratory diseases

An impressive amount of data supports the effects of air pollution on respiratory diseases both in terms of mortality and morbidity (2-4). However, aeroallergens have been rarely included among pollutants and their possible effects are often neglected. Brunekreef et al were the first in 2000

to report a statistical association between the day-to-day variation in pollen concentrations and that of deaths due to cardiovascular disease, chronic obstructive pulmonary disease (COPD), and pneumonia (5). The study was performed about the years 1986 to 1994 in the Netherlands and daily pollen levels were considered for the most frequently occurring taxa (Poaceae, *Betula*, *Quercus*, *Fraxinus*, *Artemisia*, and *Rumex)* from two stations (Leiden, west and Helmond, south). The relation between daily mortality and airborne pollen concentrations was modelled using Poisson regression with generalized additive models. Results were also adjusted for long-term and seasonal trends, influenza morbidity, ambient temperature, relative humidity, day of week and holidays. Furthermore, the authors analyzed airborne pollen concentrations on the same day as mortality was measured, the previous day, the day before that, and on the 7 days preceding the day of the death counts.

One can regret that Brunekreef's paper is reduced to a short research letter, in which the results are not completely exposed. For instance, the authors do not report the average age of the subjects died, nor it was compared to the average age of deaths in season and off-season grasses. The main findings were nevertheless as follows:

- Poaceae weekly concentrations were particularly associated with daily deaths due to COPD and pneumonia.
- There was a fairly consistent dose-response relation; the weeks with the highest Poaceae pollen averaged concentrations (>135 grains per m^3 air and per day) had a relative risk (RR) of 1.150 ($CI_{95\%}$=1.079-1.225) for mortality due to COPD and 1.168 ($CI_{95\%}$=1.077-1.266) for mortality due to pneumonia.
- *Betula* and *Rumex* were also positively, but more weakly associated to respiratory mortality.

None of these findings was confounded by air pollution (particles smaller than 10 μm in diameter, black smoke, sulphate and nitrate aerosols, nitrogen dioxide, sulphur dioxide, or ozone). Associations between chemical air pollution and mortality were also not confounded by pollen.

More recently, several papers tried to verify and clarify Brunekreef's study, at least about respiratory diseases. For example, a symmetric case-crossover analysis, including pollen levels of Asteraceae, Betulaceae, Cupressaceae, Chenopodiaceae, Ericaceae, Fagaceae, Myrtaceae, Oleaceae, Pinaceae, Plantaginaceae, Platanaceae, Poaceae, Polygonaceae, Salicaceae and Urticaceae, performed in the city of Vigo (Northwest Spain) provided confirmation of a short-term relationship between pollen levels of *Betula*, Chenopodiaceae, *Corylus* and *Alnus* and the risk of telephone requests for emergency medical attention in the case of respiratory causes during the period 1996-1999, even though no interaction was in evidence between pollen and chemical air pollutants (6). Interestingly, the association was statistically significant at lag 0 for Chenopodiaceae, at lag 2 for *Corylus* and *Alnus* and at lag 3 for *Betula*, whereas no relationships were found at lag 1. Quantitatively, a rise in *Betula* levels from the 95th to the 99th percentile was associated with an increase of 30.56% ($CI_{95\%}$=30.02-31.10%) at 3 days in the medical emergency calls for respiratory causes. Unfortunately, in this study the authors did not always clearly differentiate between allergic and non-allergic respiratory diseases.

In Darwin (Australia), positive linear associations were detected between hospital admissions for total respiratory diseases and for COPD in the period from April 2004 to November 2005 and total pollen counts, without lag effect. But no convincing evidence was found for relationships for total pollen with asthma and respiratory infections. This finding of an association between pollen concentrations and respiratory hospital admissions that could not be explained by asthma admissions suggests that ambient airborne pollens might have a wider public health impact than previously recognized. When individual taxa were investigated, associations were the strongest in relation to Myrtaceae pollen, the dominant tree taxon in the region. However, the fact that the positive associations observed for two taxa as abundant in the area as Poaceae and *Platanus* did not reach statistical significance, can raise some doubts about the real role of pollen in non-allergic situations (7).

Another study, published by Burney et al (8), shed a new light on the intrinsic (i.e. non-allergic) asthma. A cohort of 297 patients using bronchodilators, aged 18-64 years, was extensively evaluated with skin prick tests in London and they were asked to report any acute respiratory events over the coming months. Small particles with a mean aerodynamic diameter <10 μm (PM_{10}) were collected and the ability of airborne particles to bind IgE from the patients was compared for particles sampled on the weekend before their reported exacerbation with particles sampled on the weekend 2 weeks before or after. A highly significant association (p=0.00089) between exacerbations and a 25% increase in IgE binding to particles collected on the previous weekend compared with the control weekends was found, even in patients with negative skin tests to grass or tree pollens, but without significant difference between sensitized and not sensitized. This observation indicates a role of unidentified allergens

in asthmatic diagnosed as intrinsic, suggesting limits in current allergy diagnostic and a possible interpretation of some findings on the effects of pollen on non-allergic diseases. However, the study does not rule out the possibility of a relationship between clinical exacerbations and meteorological conditions or overlapping viral or bacterial infections.

Effects on cardio- and cerebrovascular diseases

As far back as 1982, Rozencwaig (9) suggested a higher incidence of cardiovascular diseases in patients with positive allergy tests, but he did not adjust for other risk factors, what may have confounded the association between allergy and the incidence of cardiovascular diseases.

It is a fact that the abovementioned study in the Netherland (5) does not allow to draw any conclusions on possible effects on mortality for cardiovascular diseases. The association with mortality was only seen for two taxa, *Betula* and *Rumex,* and authors did not display results divided by diseases. On the other hand, high Poaceae pollen counts were not associated to mortality from cardiovascular diseases. Similarly, in the already cited study covering patients who made medical emergency calls in Vigo (6), elevations in pollen levels did not increase medical emergency calls because of cardiovascular causes.

However, a cohort followed for 30 years in a rural and an urban area of the Netherlands has shown that two objective allergy markers such as peripheral blood eosinophilia and positivity on skin-prick tests for common aeroallergens were related to increased mortality due to cardiovascular death (10). Defined as ≥275 cells/mm^3 of blood, eosinophilia was associated with an increased risk for death from both ischemic and non-ischemic cardiovascular disease (RR=1.73; $CI_{95\%}$=1.37-2.18), independent of sex, age, smoking habits, body mass index, and geographical location. These results were not restricted to asthmatics. In contrast, the presence of positive skin tests was not associated with increased mortality from all cardiovascular diseases (RR=1.03; $CI_{95\%}$=.75-1.42) or any of the subgroups. The association between eosinophilia and cardiovascular mortality was not different for subjects with and without positive skin tests.

As regards cerebrovascular diseases, Low et al analyzed the effects of numerous environmental variables, including pollen counts, on hospital admissions for stroke in New York (11). Using a statistical time series modelling technique with stroke admissions as the response variable, the authors found a relatively small, but independent and statistically significant exacerbating effect (p=0.0341) of grass pollen concentrations used as explanatory variables on stroke incidence. Unfortunately they did not provide any hypothesis supporting this observation, apart from the fact that alveolar inflammation is proposed as the mechanistic link. Similarly in the Netherlands, subjects with peripheral blood eosinophilia have increased mortality from cerebrovascular disease (RR=2.30; $CI_{95\%}$=1.39-3.79), after adjustment for major risk factors (10). Hay fever was also interpreted by Matheson et al (12) as a potential risk factor for stroke: during a 4.4-year period in South Carolina, patients with a history of allergic rhinitis had an unadjusted hazard ratio of 1.72 ($CI_{95\%}$=1.08-2.27) for stroke versus patients without allergic rhinitis. Risk of stroke remained significant (hazard ratio, 1.87 [$CI_{95\%}$= 1.17-2.99]) after controlling for age, sex, race, smoking status, body mass index, diabetes, hypertension, alcohol use, and hyperlipidemia. The authors suggested the mechanism to be the systemic inflammation found in those with allergic rhinitis. Yet, Ng et al put forward an additional explanation, i.e. lymphoid hypertrophy with obstructive sleep apnoea (OSA), for the increased risk. Indeed, it is now well accepted that allergic rhinitis is associated with increased risk of OSA in adults and children and that adults with OSA have an increased risk of cerebrovascular disease independent of atherosclerotic risk factors (13, 14).

Effects on psychiatric diseases

The seasonal trend of various psychiatric diseases has been consistently reported, but its causality is still poorly understood. In this view, several papers investigated the possible associations with the pollen season which is overlapping the seasonality of some psychiatric diseases. Two complementary studies, respectively empirical and experimental, showed a neurobehavioural regression in children with autistic spectrum disorders (ASD) or attention deficit hyperactive disorders (ADHD), not only during pollen seasons (15) but also after nasal challenge with oak tree, timothy grass and ragweed pollen (16). The dose insufflated into each nostril was 25mg (±15%) of each pollen, what is probably a disturbing procedure for any type of individual, suffering or not from psychiatric disorders. During experimental pollen exposure, 55% of children with ASD and 67% of children with ADHD, or a total of 60% of children regressed signifi-

cantly (p<0.01) from their baseline. There was no correlation with the child's allergic status (IgE, skin tests and RAST) or allergy symptoms. The same effect was observed in allergic and non-allergic children. The regression was not associated with respiratory symptoms. Authors suggested, although they did not yet empirically test, an unknown non IgE-mediated mechanism underlining this relationship.

But, the most numerous studies are about suicide or suicide attempt, particularly thanks to the University of Maryland School of Medicine at Baltimore. A strong and highly replicated seasonality of suicide in late spring and, less consistent, in late summer and early fall is well known (17). For this reason, Postolache et al performed an epidemiologic study analyzing 2417 suicides in the tree pollen season and 1811 in the ragweed season for the continental US and Canada in the period 1995-1998. They found a two-fold increase in the rate of non-violent suicides among younger females during intervals of high tree pollen, in comparison to similar intervals of low tree pollen ($CI_{95\%}$=1.3-3.0); there was no difference between the postpollen period and the prepollen period (18). The association was thus found only for non-violent suicides, only in females, and only for tree pollen (but not for ragweed pollen). While these result may have been confounded by a number of biological and psychosocial factors (such as impact of feeling sick), acting during the allergy season on individuals and their social support systems, two possible explanations were proposed: the side-effect of antiallergic drugs (pseudoephedrine, antihistamines and corticosteroids), which may worsen prosuicidal factors such as night-insomnia, day-somnolence, agitation, anxiety, impulsivity, and cognitive disturbance (19); or a mechanism linked to an increased expression of cytokines during the immune activation. Actually, both hypotheses appear rather weak. Nevertheless, four points require careful thought:

- Firstly, if there is insufficient data to prove any link between the other medications used to treat allergy and suicidality, systemic (but not topical) corticosteroids used for severe symptoms have been really associated with manic and depressive episodes and mixed mood states (20). Moreover, on June 12, 2009 the US Food and Drug Administration issued a warning raising concerns about the suicidality potential of montelukast (trade name Singulair®) and other leukotriene receptor antagonists (LTRA) (21).
- Secondly, the intranasal pathway is well known as a direct route of communication between the environment and the brain: this pathway is currently used for the delivery of several experimental therapeutic peptides and vaccines, including both small molecules and macromolecules, because it bypasses the blood brain barrier. But it is also a route of entrance to the brain for many infectious, allergic and pollution agents (22, 23). The inflammatory processes triggered in the upper respiratory tract by these agents are positioned to influence the immune response of the brain and therefore, influence its function and alter behavior. Several clinical and epidemiological studies found an association between inflammatory factors affecting the intranasal pathway and neurological disorders such as multiple sclerosis, Alzheimer and Parkinson diseases as well as mental disorders including anxiety and mood disorders. However the mechanisms of interaction between the immune response in the nasal epithelium and the brain are largely unknown (23).
- Thirdly, another mechanism linking allergic inflammation, depression, and suicide has been determined. Indeed, Reeves et al outlined the role of alcohol, that is a well-established risk factor for adolescent suicide, in inducing phosphorylation and rearrangement of tight junction proteins of the blood-brain barrier (BBB) resulting in increased "leakiness", i.e. passage of cells and molecules. Of course, many authors proposed for a long time that allergic inflammation influences depression-related brain function via molecular and cellular mediators, but those mediators have a very limited access to the brain when the BBB is intact. Yet, alcohol intake disrupts BBB, allowing increased brain exposure to cellular mediators of allergy, especially in youth when alcohol use starts (24).
- Lastly, it has also been established in Brown Norway rats that sensitization and exposure to aeroallergens induces anxiety-like and aggressive behaviours as well as allergy-related helper T-cell type 2 (Th2) cytokine gene expression in the prefrontal cortex (20). Thus, it is possible that sensitization and exposure to aeroallergens, which peaks in spring, may be conducive to seasonal exacerbation of suicide risk factors such as anxiety, depression, hostility/aggression, and sleep disturbance. The recent report of Th2 (allergy-mediating) cytokine expression in the orbitofrontal cortex of suicide victims should lead to future studies to test the hypothesis that mediators of allergic inflammation in the nasal cavities may result in Th2 cytokine expression in the brain, influencing affect and behavioural modulation (20).

Other studies showed a highly significant relationship

($p<0.001$) between high pollen season and self-reported non-winter seasonal affective disorder (SAD), characterized by depression in summer and remission in fall and winter (25). The survey was conducted among college students at local universities in Washington, DC. However, the sample included only African American and African students and, therefore, the results may not be applied to the entire population. The Seasonal Pattern Assessment Questionnaire (SPAQ) is not a definitive tool to assess seasonality, and self-reported mood-worsening with high pollen counts relies on recollection. The non-winter SAD concept has not been previously established. Moreover, the study was only based on questionnaire and patients were not tested for pollen sensitization: no direct measures of depression scores or pollen counts were collected. Consequently, the study should be considered as preliminary in light of its limitations. It is nevertheless a fact that the findings confirm certain results of the oldest study about this question, which used an ethnically diverse sample (26).

The following observations are supported by the literature published so far:

- The rates of depression, anxiety, and sleep disturbance (suicide risk factors) are greater in patients with allergic rhinitis than in the general population.
- The rate of allergy is greater in patients with depression.
- Patients with a history of allergy may have an increased rate of suicide[1].

However, it remains unknown if these associations are true or spurious, and if true, if they represent trait (vulnerability)- level relationship or if mood-states are involved, i.e. if there is adequate evidence to suggest that exposure to allergens might trigger mood changes in vulnerable individuals. In another study, confirming the relationship between tree pollen and changes in mood in patients sensitized to those pollen, Postolache et al suggested a connection between allergy and depression decompensation rather than between pollen and depression (28).

To sum up, allergy can influence mood by several potential mechanisms. There may be somatic changes such as discomfort caused by allergic inflammatory processes in the upper airway that may affect well being. This situation may lead to other possible mediators affecting mood, such the use of medications such as corticosteroids or LTRA, or disturbance of sleep caused by multiple factors including obstruction of the airways. The release of inflammatory mediators including cytokines is one likely mechanism that may promote the worsening in mood. This mood worsening can occur by either acting directly in the brain or through other pathways such as interactions with the HPA-axis and/or the IDO enzyme. Cytokines have been shown to induce depression and anxiety. The findings of Postolache et al relating allergic symptoms with depression scores may be explained in part by the release of cytokines during allergic reactions (28). *In vitro* studies have also shown that certain human polymorphisms increase the expression of cytokines including TNF-α, IL-13, and IFN-γ (29). In addition, certain cytokine polymorphisms increase susceptibility to allergic disease such as asthma (30). Moreover, allergic symptoms have been correlated with the amount of cytokines released during some allergic reactions. Thus it is possible that depression scores in some individuals may reflect the increased amount of cytokine release during allergic processes. This issue is a matter to be clarified with future investigations.

General discussion

To our knowledge, apart from an attempt to favour a holistic view of pollen and its impact on human health (1), this is the first time that the effects of pollen on non-allergic diseases are reviewed. Actually, studies are sparse and focused on different diseases but this relationship deserves a discussion for several reasons.

First of all, it is now widely accepted that pollen grains are not only releasing proteins and glycoproteins eliciting specific immune responses, but contain pro-inflammatory substances, such as NADPH oxidases and oxylipins; the latter is part of the so called "pollen-associated lipid mediators" (PALMs) which also include phytoprostanes, an immunomodulatory substance (31). These findings suggest a proinflammatory and immunomodulatory effect of pollen which can be associated or not with the IgE-mediated pathway. Thus, we could hypothesise that these substances might be able to exert some effects in non-allergic diseases, other than acting as adjuvant in the IgE-mediated reactions in allergic patients.

[1] It is however important to note, according to Okusaga et al (27), that seropositivity for influenza A ($p=0.004$), B ($p<0.0001$) and coronaviruses ($p<0.0001$) are also associated with history of mood disorders, but not with the specific diagnosis of unipolar or bipolar depression. Seropositivity for influenza B is significantly associated with a history of suicide attempt ($p=0.001$) and history of psychotic symptoms ($p=0.005$). It follows that mood disorders and suicidal behaviour may be associated with common respiratory viruses as well as with pollinosis.

Secondly, some of the abovementioned papers involve a large number of patients and use robust statistical methods. Finally, submicronic and paucimicronic particles derived from pollen are thought to constitute the Particulate Matter (PM) which has been associated with health effects in an impressive amount of studies both experimental and epidemiological (32). For this reason, future research should be addressed to evaluate the role of pollen-derived particles in the PM-related health effects.

At the end of this analysis, it is, however, necessary to point out that papers reviewed here have some indisputable limitations. In the first place, several of these papers (5, 10, 15, 16…) have not been replicated by any other researcher in the last years, what must incite us to be cautious. Moreover, one can never be absolutely certain that all the potential confounding variables have been correctly controlled; this remark applies namely to weather and air-pollution variables, where interactions are complex. So, if the data used by Hanigan et al (7) have been adjusted for both air temperature and fungal spore concentrations, perhaps the correlation between Myrtaceae pollen counts and respiratory exacerbations would be become insignificant. Then, studies on non-allergic respiratory diseases (7, 8) have the well-known diagnostic limitations which don't allow a clear distinction between asthma and COPD. Even when respiratory infections are taken into consideration (7), it is not easy to exclude an underlining respiratory allergy. Regarding the effects on cardiovascular and respiratory mortality, the study (5) is rather well conducted. However, while the airborne pollen concentration often shows a great variability from a site to another, data from two pollen stations seem insufficient for a nationwide study on mortality, especially since deaths are related to the whole territory of the Netherlands.

Discussion of findings on non-respiratory diseases is challenging. In the case of stroke, pollen was included in an extremely large number of environmental variables (11), making an evaluation of each result very difficult. Pollen is not always clearly distinguished from other aeroallergens. Now, positive associations were noted for the period 1992 to 1996 between cardiorespiratory emergency department visits in Saint John, Canada, and Ascomycetes, *Alternaria* or small round fungal spores, rather than between these visits and pollen (33).

Interestingly, a significant number of studies are focused on psychiatric disorders, following consistent observations of a seasonality of some diseases. The first limitation is that research team is the same in nearly all the studies. Secondly, subjects are not extensively screened for allergic diseases in most studies and no information on atopy was available in the main study on suicides in the US (18).

Besides, the here studied diseases do not exhaust the entire spectrum of diseases favoured by either allergenic pollen or pollen allergy. So, Ferencz et al (34) considered in Hungary postmenopausal women suffering from pollen-allergy. The patients without treatment had a slightly lower bone density than their non-allergic counterparts. Moreover, the rate (34.9%) of prevalent low-energy fractures (distal forearm, hip, and clinical vertebral fractures) in untreated allergic patients was almost triple that observed in non-allergic women (13%, chi_2 p=0.003). In conclusion, the authors suggested that pollen-allergy, overall associated with obesity, is a risk-factor for a high prevalence of low-energy fractures among postmenopausal women.

It may again be added that some relationships between cancers and allergies have intrigued researchers and health care providers for five decades. Sherman et al (35) located 148 papers published from 1955 through 2006 that reported results of 463 studies of relationships between patients' histories of 11 specific allergies and cancers of 19 tissues and organ systems, and 183 studies of patients' histories of multiple allergies in relation to various types/sites of cancers. Analyses of these studies revealed that more than twice as many studies reported inverse allergy-cancer associations as reported positive associations. Inverse associations with allergies were particularly common for cancers of tissues and organ systems that interface with the external environment (mouth and throat, skin, lung among non-asthma sufferers...) compared to cancers of tissues and organ systems that do not interface with the external environment. These results are consistent with a prophylaxis hypothesis. The IgE system and its associated allergy symptoms may serve a common protective function: the rapid expulsion of pathogens, dangerous natural toxins, and other carcinogenic antigens before they can trigger malignant neoplasia in exposed tissues.

Conclusion

Current knowledge is still insufficient to draw a conclusion on the effects of pollen on non-allergic diseases. On one hand, experimental studies showing a proinflammatory and immunomodulatory activity of pollen support the hypothesis of a non-IgE mediated effect on human

health. Even if with several limitations and methodological shortcomings, some epidemiological observations are consistent with the experimental data. On the other hand, most part of findings is provided by studies on respiratory and psychiatric diseases which present some diagnostic difficulties and limitations. And last but not least, all findings reviewed in this paper have not been sufficiently reproduced so far and are not entirely convincing.

Consequently, further research is needed at clinical, epidemiological, animal and postmortem tissue levels to clarify the complex role of pollen in human health, which goes probably beyond the allergic diseases. Experimental studies should identify the role of pollen-derived particles in the context of PM and their effects on human health. Moreover, epidemiological studies should be specifically designed by a multidisciplinary research team, with the aim of confirming the association between pollen counts and diseases. The advances in the field of airborne allergens detection could contribute to distinguish the effects of allergens from those of other non-allergenic proteins of pollen (36).

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