

Hypothesis: urbanization and the allergy epidemic – a reverse case of immunotherapy?

A. Linneberg*

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Urbanization is a prominent feature of western lifestyle and has consistently been associated with higher prevalence of allergy. One somewhat neglected observation is that migration from a low-risk (rural) to a high-risk (urban) area may lead to increased risk of developing allergy. Data from the Copenhagen Allergy Study (1), a prospective population-based study of adults, show that persons who had migrated to Copenhagen (the most urbanized area in Denmark) had a significantly increased risk of developing allergy over an 8-year observation period compared with those persons who had lived their whole life in Copenhagen without developing allergy (Table 1). This finding suggests that changes in environmental (or lifestyle) factors associated with urbanization, although these changes take place in adult life, induces allergy development (or 'loss of tolerance').

Allergen-specific immunotherapy (SIT) has been known for more than 100 years and the effect is well documented, in particular, for grass pollen allergy. Thus, it is a scientific fact that high doses of grass pollen allergens induce tolerance to grass pollen. It is a less-recognized fact that SIT may have nonspecific effects in terms of preventing the development of

Migration from rural to urban areas increases risk of allergy.

Table 1. The association between migration to Copenhagen and the incidence of skin-prick reactivity (≥ 3 mm) to at least one of 10 inhalant allergens in a 8-year follow-up study of 15–69-year olds

	Incidence % (n/total n)	Risk*
Subjects who had lived all their life in Copenhagen	7.0 (12/171)	1 (reference)
Subjects who had migrated to Copenhagen	14.3 (33/231)	3.4 (1.6–7.2)

*Odds ratio (95% confidence interval) adjusted for sex, age, smoking, and alcohol consumption.

new allergies (2). Although SIT has long-term effects, discontinuation of SIT may, in some patients, result in decreased tolerance and re-occurrence of allergic symptoms.

Discontinuation of SIT might work as a model for the situation when persons migrate from a low- to a high-risk area (from low to high allergen exposure). Westernized and urbanized populations are probably exposed to lower concentrations of allergens such as pollens. They spent more time indoors where pollen concentrations are lower compared with the outdoor environment in a rural area. Lower exposure to allergens may lead to loss of tolerance and development of allergy to pollen. Theoretically, when people migrate from rural to urban areas, they lose some of their daily doses of pollen allergen, which might explain why they apparently tend to develop allergy (or lose tolerance). One may label this phenomenon 'a reverse case of immunotherapy'. It is also possible that bacterial antigens have nonspecific effects on the immune system and these are mediated through mechanisms similar to those of SIT (bacterial immunotherapy) (3).

It is almost a paradigm in allergology that allergen avoidance is beneficial, e.g. in house dust mite-allergic patients. Although it is evident that dust mite-allergic patients develop symptoms when they are exposed to sufficient amounts of dust mite, meta-analyses have not been conclusive about the effect of measures aiming at reducing

house dust mite exposure (4). It has furthermore been suggested that high concentrations of cat allergens in the home induce tolerance (5). Recently, Barbi et al. (6) presented a fatal case of loss of tolerance to milk proteins following elimination diet. They proposed that in some patients avoidance of allergens may worsen the condition. Indeed, it is a paradox that the highest prevalence of hayfever (pollen allergy) is seen in the most urbanized areas where people are probably exposed to lower concentrations of pollen allergens. It seems as if the paradigm that increased exposure to allergens leads to increased prevalence of allergy is being challenged.

In conclusion, it is hypothesized that the association between urbanization and increased risk of allergy may be explained by a decreased exposure to allergens such as pollens leading to lower tolerance to pollens. Through nonspecific effects on the immune system, this may also lead to lower tolerance to allergens in general increasing the susceptibility to allergic disease: a reverse case of immunotherapy! The rising trends of allergy may thus, in part, be explained by changes towards urban lifestyle including exposure to lower doses of allergen due to more time spent indoors and away from areas abundant in natural allergen sources.

*Research Centre for Prevention and Health
Glostrup
Denmark
E-mail: linneberg@dadlnet.dk;
alli@glostruphosp.kbhamt.dk

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Common variable immunodeficiency with seasonal variation

I. S. Choi*, S.-Y. Lim, K.-M. Kim, Y.-W. Cho

Key words: allergy; common variable immunodeficiency; hypogammaglobulinemia; immunoglobulin G.

Common variable immunodeficiency (CVID) is characterized by pan-hypogammaglobulinemia and recurrent sinopulmonary infection. As both immunoglobulin (Ig)G and the other

immunoglobulin isotypes, including IgE, are low (1) and the Th1 cytokines interleukin (IL)-12 and interferon (IFN)- γ are elevated in many patients with CVID (2), it is speculated that IgE-mediated allergic diseases occur rarely in CVID patients.

However, Schwartz et al. (3) reported on an adult with co-existing allergic bronchopulmonary aspergillosis and CVID. Here, we present a case of CVID with seasonal allergic symptoms and decreased serum IgG levels during the allergic season.

SJW was a 32-year-old man who had suffered from recurrent pneumonia since the age of 23. He was diagnosed with CVID at another hospital and had received immunoglobulin replacement therapy regularly. He was transferred to our hospital in late-1996. At presentation, T3, T4, T8, B, and natural killer (NK)

cells were 83.0, 7.6, 70.5, 6.7, and 6.8%, respectively; IgG, IgA, and IgM levels were 508, <31, and <29 mg/dl, respectively; IgE was <27.4 IU/ml. Human IgG (25 g) had been administered only intermittently, at 2–3-month intervals, for economic reasons. Although the patient rarely needed antibiotics, he complained of sneezing, rhinorrhea, and occasional severe cough at night during spring. Wheezing was heard in his chest at times.

The patient told us that he believed that his serum IgG level was lower in spring. In a review from his chart, his allergic symptoms were recorded almost exclusively from February to May (spring). The average serum IgG level in the years 1997–2003 that was corrected considering the irregular interval of the replacement therapy [median: 69.5 days in spring and 82.0 days from August to November (other seasons)], was significantly lower in spring than in other seasons (228.7 ± 50.6 vs 289.8 ± 73.3 mg/dl, $P = 0.018$; Fig. 1). The serum total IgE level measured seven times over the past 7 years, including during spring, remained undetectable.

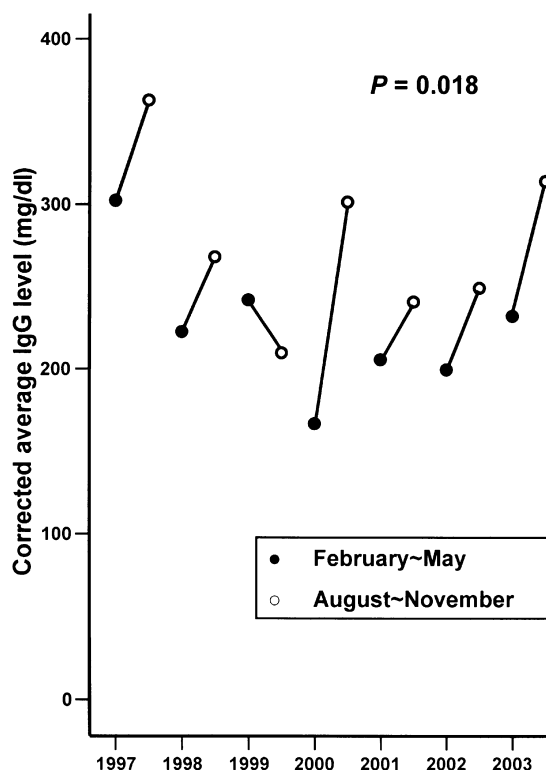


Figure 1. The corrected average serum immunoglobulin G level from February to May was significantly lower than that from August to November in an adult patient with common variable immunodeficiency.