

Environmental priming influences allergen-specific nasal reactivity

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Background Preceding mucosal response to one allergen leads to the priming of the nasal mucosal response to another allergen. This study aimed to determine whether environmental allergens, especially ubiquitous animal dander, can induce nasal priming.

Methods We investigated 26 grass-pollen-allergic subjects with additional sensitization to other aeroallergens. We performed continuous allergen challenge for 2 h with 1500 *Dactylis glomerata* pollen/m³ in the Vienna challenge chamber. The nasal flow at 150 Pa was examined, and subjective scores were obtained every 15 min. Statistical analysis was calculated from the area under curve of nasal flow reduction by Student's *t*-test and the Mann-Whitney *U*-test. Alpha was 0.05.

Results In subjects with positive cat-dander RAST (class of ≥ 3), besides grass-pollen allergy, the specific nasal allergic reaction to *Dactylis* challenge was significantly pronounced ($P < 0.01$), and an earlier onset of reaction was evident. The same results were obtained with additional sensitization to dog dander ($P < 0.05$). Concomitant sensitization to mugwort also led to escalating symptoms ($P < 0.05$).

Conclusions These results indicate that a specific nasal allergic reaction is augmented by environmental priming caused by ubiquitous animal dander and possibly is influenced by the daily use of spices.

Key words: allergic rhinitis; environmental allergens; grass-pollen allergy; priming; rhinomanometry.

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Most allergic patients are not sensitized to one allergen only. They show polysensitizations to various aeroallergens with distinct clinical expression. Influences of various aeroallergens in subsequent seasons are known to induce priming effects (1). Priming leads to an earlier onset and aggravated symptoms in subsequent allergen exposures, due to a higher load of allergenic effector cells in the nasal mucosa (2). Previous studies demonstrated that priming was specific for the side of the nose challenged, disappeared when exposure was stopped, occurred during seasonal exposure, and was not specific for the antigen inhaled (3). Therefore, perennial allergens also should induce nasal mucosa priming. The initial therapy of allergic disorders is to avoid allergen contact. Especially for house-dust mites, (HDM) a great variety of mite-allergen controls in homes has been proven effective (4, 5). Recent studies show a high Fel d 1 and Can f 1 concentration in school dust and homes without pets (6). They show that sufficient allergen restriction is not possible for these allergic patients. This fact has to be considered in diagnosis

and therapy of specific allergies as well, as it could have a great impact on nasal challenge experiments. In recent literature, there is no investigation proving that environmental allergens influence specific allergic reactions.

We chose to test this hypothesis in patients highly sensitized to grass pollen and polysensitized to other common aeroallergens, outside the grass-pollen season when they had no clinical signs of seasonal nasal allergic reaction. Our objective in this study was to determine whether environmental (perennial) allergens in polysensitized patients affect specific reactions to grass-pollen challenge in terms of nasal flow and overall subjective condition, when subgroups of the study group were evaluated for their other sensitizations.

Material and methods

Patients

Twenty-six grass-pollen-allergic patients (18 men, mean age 27 years) volunteered to enter the study.

Table 1. Patients' additional sensitizations. All patients were sensitized to grass pollen (*Dactylis glomerata*). Listed are additional sensitizations (mean values and standard deviation) to common aeroallergens in our environment. "Fungal" covers *Cladosporium herbarum* and/or *Alternaria tenuis*

	Patients <i>n</i> =26	RAST class (mean)	RAST class (SD)
Grass pollen	26	3.8	0.8
Birch pollen	16	3.5	1.2
Mugwort pollen	9	2.2	0.5
House-dust mite	10	3.0	0.9
Fungal spores	5	2.7	1.0
Cat dander	14	3.3	1.0
Dog dander	9	2.9	0.5

They were symptomatic during the grass-pollen season and were free of symptoms for the rest of the year. A positive case history (>2 years), positive skin prick test (SPT) to *Dactylis glomerata*, and a RAST class of ≥ 2 (mean 3.84) to g3 and g12 were obtained, as well as a positive conventional nasal allergen-challenge-proved reaction to *D. glomerata*, performed more than 2 months before starting the study. Additional sensitization to other common airborne allergens was determined (Table 1).

Before entering the study, patients gave informed consent to the ethics committee-approved study protocol.

None of the patients had nasal anatomic aberrations, infection of the upper respiratory tract within the last 4 weeks, systemic or topical therapy with antihistamines or steroids within the last 4 weeks, bronchial hyperreactivity, or a case history of asthma. Female patients were allowed to enter the study only if taking oral contraceptives.

Allergen challenge

All patients were challenged while asymptomatic outside the grass-pollen season (Dec/Jan).

The allergen exposure was carried out as a reproducible and physiologic long-term allergen challenge in the Vienna challenge chamber (VCC) (7). The VCC is a tool that enables us to perform long-term allergen challenges in conditions close to those of natural allergen exposure during the pollen season. It is a cubic room in which up to 12 persons can be challenged simultaneously under controlled and reproducible conditions. Patients are exposed to native *D. glomerata* pollen (Allergon AB, Sweden) in a concentration of 1500 pollen grains/m³ for 2 h continuously. The pollen is added to the intake of the air-conditioning system. The homogeneous distribution of pollen grains is certified (8). The amount of pollen in the air is determined every 5 min as grains/m³ by a modified

Hirst-type trap (Burkard Ltd, UK) (9). This enables us to keep the allergen concentration stable inside the chamber. The indoor climate (25°C air temperature and 30% air humidity) is controlled and kept constant by an air-conditioning system.

Parameters obtained

The objective parameters were as follows.

Nasal obstruction. This is measured by active anterior rhinomanometry. We use a computer-assisted system consisting of a rhinomanometer (MP441 J. Ganzer KG, Germany) connected to a PC (IBM, USA). Patients are measured in an upright, sitting position, with a full screen mask and sponge nozzles. This enables us to take a measurement within 1 min. The primary objective is to reach nasal flow at 150 Pa, according to the international standards (10). In order not to influence nasal mucosa by mechanical irritation, which could interfere with nasal obstruction measurements, we did not attempt to obtain nasal cytologic specimens.

Lung function. This is measured by spirometry for safety reasons. We use a Vitalograph spirometer. Measurements are performed every 30 min. If the FEV₁ decreases by 20% from the initial measurement, the patient is withdrawn from the study.

Subjective parameters

The overall subjective condition is recorded with a standardized 100-mm visual analog scale (VAS), which patients have to fill in every 15 min.

Statistical evaluation

The target parameter is the area under curve (AUC) of the nasal flow decrease at 150 Pa. After the presuppositions (normal distribution, homogeneity of variances) were tested, a Student's *t*-test or Mann-Whitney *U*-test was performed.

Results

Our group of polysensitized allergics showed a mean of three sensitizations additional to their grass-pollen allergy. Symptoms developed immediately after exposure to indigenous airborne grass pollen in the VCC. All of the challenged patients showed the typical prolonged immediate reaction pattern of nasal flow development (11). The nasal

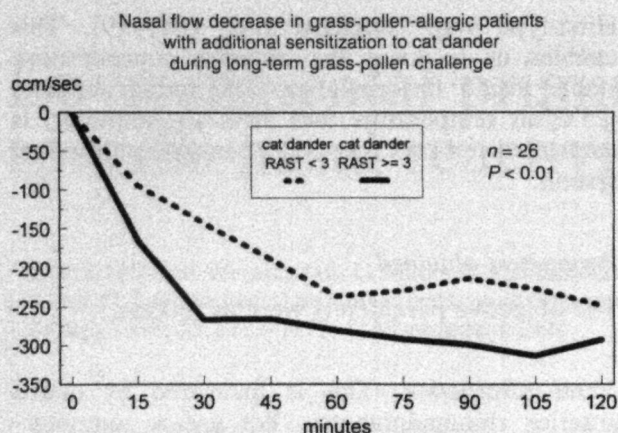


Fig. 1. Full line indicates nasal flow development in grass-pollen-allergic group additionally sensitized to cat dander (RAST class of ≥ 3). Dotted line shows nasal flow development in other group (RAST to cat dander of < 3). Reaction of highly cat-dander-positive group was more pronounced, and earlier onset of reaction is visible ($P < 0.01$).

flow decreased continuously after the beginning of the challenge, reaching a minimum flow after 60 min, which was then followed by a plateau phase. Of the 26 challenged patients, 16 were allergic to cat dander as well as grass pollen. In the patients with positive cat-dander SPT (wheal diameter of > 4 mm) as well as positive cat-dander RAST (class of ≥ 3) the specific nasal allergic reaction to grass-pollen challenge was significantly pronounced ($P < 0.01$), and an earlier onset of the plateau phase was evident, compared to those with no or less sensitization to cat dander (Fig. 1).

Patients with additional sensitization to dog dander (9/26, SPT; mean wheal diameter of > 4 mm) besides the grass-pollen allergy presented similar results. The nasal reaction to the same amount of allergen (1500 *Dactylis* pollen grains/m³) was more pronounced ($P < 0.05$), reaching a minimum nasal flow rate at 60 min and remaining at that reduced level (Fig. 2).

Additional hypersensitivity to mugwort (*Artemisia vulgaris*) in grass-pollen allergic patients (9/26) also led to higher nasal reactivity, as described before. A minimum of nasal flow was reached after a 60-min grass-pollen challenge. The mugwort-sensitized patients also showed earlier onset and increased nasal reaction ($P < 0.05$) (Fig. 3).

Additional sensitization to birch pollen and fungal allergens did not lead to any significant difference in reactivity to specific grass-pollen challenge. Furthermore, concomitant mite allergy did not seem to influence nasal flow development.

No changes in lung-function parameters such as FEV₁ and PEF could be detected throughout the challenge session. No participant of the study had to be excluded.

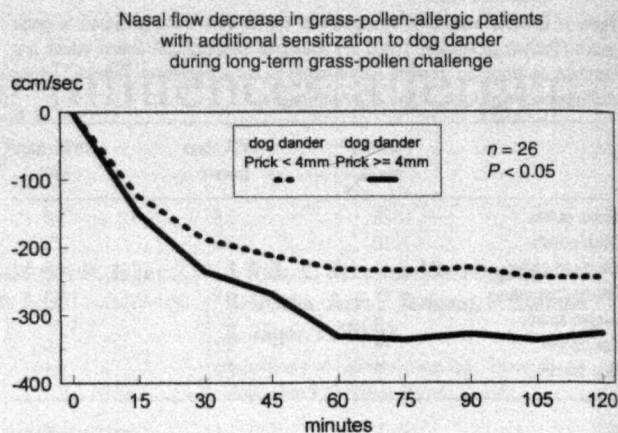


Fig. 2. Full line indicates nasal flow development in grass-pollen-allergic group additionally sensitized to dog dander (SPT: mean wheal area of ≥ 4 mm²) and is significantly different ($P < 0.05$) from nasal flow development in other group (mean wheal area of < 4 mm²) indicated by dotted line.

The subjective complaints reported by VAS showed good correlation with the nasal flow results.

Discussion

Much information on the allergic response has been acquired by challenging asymptomatic allergic subjects intranasally with allergen. Our challenging method in the VCC is equivalent to the continuous allergen challenges occurring during seasonal exposure under controlled conditions (7).

To objectify nasal reaction to allergen exposure, we used measurement of nasal flow by active anterior rhinomanometry, as advocated by the international committee on objective assessment of the nasal airway as a reliable method for measuring these symptoms (12). Nasal flow can be measured

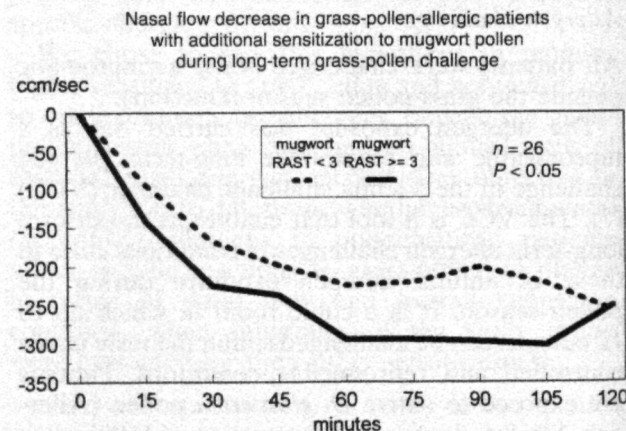


Fig. 3. Full line indicates nasal flow development in grass-pollen-allergic group additionally sensitized to mugwort pollen (RAST class of ≥ 3). Dotted line shows nasal flow development in other group (RAST to mugwort of < 3). Reaction of highly mugwort-pollen-sensitive group was more pronounced, and earlier onset of reaction is visible ($P < 0.05$).

rapidly and reproducibly with a small method error by computer-assisted active anterior rhinomanometry (13). Recent investigations showed that difficulties in interpreting rhinomanometric results could occur, caused by the effect of physiologic phenomena (14). In our study, we performed repeated measurements of nasal flow during the 2-h challenge and could show good correlation between subjective and objective measurements, as reported in previous studies (15, 16). Rapid changes in nasal flow influencing the trend in flow development were not detectable in our patients.

Priming is an increase in the reactivity of the nasal mucosa that may follow allergen exposure (3), and is linked to eosinophil influx, as previously described (16). Therefore, we decided not to attempt to obtain nasal specimens, in order not to influence nasal flow measurements.

The present investigation was directed forward to evaluate the priming influence of environmental allergens on specific nasal challenge tests in polyallergic subjects.

During continuous allergen exposure, all grass-pollen-sensitized patients showed the same reaction pattern to grass-pollen exposure. Nasal obstruction began immediately after exposure to the allergen and reached a maximum extent after 60 min, remaining in a plateau phase afterward until the end of continuous, long-term allergen provocation testing. The development of subjective complaints showed the same pattern and therefore seemed to be mainly related to nasal obstruction (17). When patients were divided into groups according to their additional sensitizations, those with additional sensitization to cat dander with RAST of ≥ 3 or additional sensitization to dog dander with wheal reaction area of $> 4 \text{ mm}^2$ in SPT showed an increased nasal blockade compared to those with minor degree of sensitization. The significantly aggravated mucosal reaction seems to be induced by priming by animal dander.

Previous investigations demonstrated the airborne levels of Fel d 1 and Can f 1 in the living rooms of homes with pets to be 100 times higher than those of mite allergens (18). These high concentrations of airborne allergens might result from high production of allergens in animals and by the spreading of their hair and dander and the raising of floor dust into the air (19). Previously published data indicate the presence of cat allergens in homes where cats have never been (20). These results suggest that sensitized patients, although they avoid pet contact, are constantly exposed to this ubiquitous allergen. Furthermore, it could be shown that the antigen is mainly produced in the intradermal hair follicle, where it accumulates and then is gradually spread to the tip on the

shaft. From there, it becomes airborne and is associated with a large range of particle sizes. Therefore, the animal dander remains longer airborne than the mite allergen, which is associated with greater particle size (21). Ohman et al. also showed that Fel d 1 and Can f 1 in floor dust are high in homes with cats and dogs (22). In contrast to mite allergens, cat allergen remains airborne in undisturbed conditions (23). People might bring cat dander into other homes and public places such as schools on their clothes, so that substantial amounts of allergen are detectable there.

Some authors estimate that the concentration may probably be high enough to cause perennial symptoms in patients with asthma who are sensitized to cat and dog (6). The increased reactivity to specific allergen challenge with grass pollen of half of our patients seemed to be caused by ubiquitous animal dander. Patients were advised to avoid direct animal contact for 3 weeks before the challenge session. Our patients were exposed to cat- and dog-dander allergens only in their everyday outdoor environment.

Seven out of 14 additionally cat-dander-sensitized patients were also sensitized to HDM allergens. Comparison of them with the other nine cat-dander-positive allergics could not detect any difference in reaction pattern. In general, this supposition seems to be supported by the results for additional sensitization to the mite allergen Der p 1. All patients were symptom free when entering the study. The homes of the patients sensitized to HDM (a total of 10 out of 26) were cleared of mite allergen by various combined treatment methods (no carpets, allergen-tight bed covers, use of acaricides, low air humidity) for years, and allergen amounts were supposed to be low. The results of nasal flow development in the group with additional sensitization to HDM failed to show any differences from those without. Comparison of the degree of sensitization to HDM and that of cat- or dog-dander sensitization showed equal mean values. The absence of a calculable priming effect suggests that the reduction of mite allergen in the patients' homes could be sufficient even in winter, although recent studies show contrary data (24).

At the same time, no differences in the group with additional sensitization to birch pollen were detectable. The birch-pollen season in our local environment is in March and April, about 7 months before the beginning of the challenge session (25). The priming effect does not seem to last that long (1). Moreover, no influence of cross-reacting food allergens seems to be effective (26, 27). In the study group, nine out of 26 patients were additionally sensitized to mugwort pollen. Those nine patients

showed increased reaction to grass-pollen challenge. The mugwort season in the year of our study ended at the beginning of September, as documented by the Austrian Pollen Information Service, just about 12 weeks before the challenge sessions. Previous studies could show a remnant effect only within hours or days. Therefore, cross-reactions from food allergens have to be considered causative, according to clinical observations that mugwort and birch-pollen allergy, and hypersensitivity to spices are frequently associated (28). Mugwort is known to share common epitopes with various vegetables, and cross-reaction syndromes are well known (mugwort-carrot-celery-syndrome) (29). Many allergens of spices and vegetables of common use (fennel, coriander, celeriac, oregano) are closely related to *A. vulgaris* allergens and hence share common epitopes (30). Subclinical allergic responses to these cross-reacting allergens might induce a priming effect even in the nasal mucosa (31).

Our results suggest that patients may respond to allergens that do not provoke clinical symptoms. The amounts of those allergens seem to be too low to cause discomfort, but it seems that the concentrations are high enough to induce subclinical allergic reactions and priming effects.

In conclusion, our data indicate that the allergic reaction to grass-pollen-induced symptoms is augmented by ubiquitous animal dander and possibly by the common use of various mugwort-related spices in patients additionally sensitized to cat dander, dog dander, or mugwort. Our results also suggest that the extent of clinical expression of rhinitis symptoms in highly polysensitized allergic patients may be due to the cumulative effect of allergens to which they are exposed in their environment.

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