

Occupational rhinitis in damp and moldy workplaces

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ABSTRACT

Background: Numerous studies confirm the association between exposure to indoor air dampness and molds and different health outcomes. Of these, upper respiratory tract problems are the most commonly reported work-related symptoms in damp indoor environments. The aim of this study was to describe a clinically investigated patient series with occupational rhinitis induced by molds.

Methods: Nasal provocation test (NPT) with commercial fungal allergens was performed in 369 patients during 1995–2004 at the Finnish Institute of Occupational Health. Of these, 60 (16%) were positive. In addition to positive NPT, the diagnosis of occupational rhinitis was based on verified exposure to molds, work-related nasal symptoms, and clinical investigations. We wanted to review the patient files of these 60 patients retrospectively, and 56 patients gave their informed consent.

Results: The mean age of the patients was 43.7 years ($SD \pm 9.5$). Fifty (89.3%) patients were women. In 23% of the patients, IgE-mediated allergy to molds could be established. Atopy significantly increased IgE sensitization to molds (OR, 10.3 [95% CI, 2.0–52.5]). The most common mold to induce occupational rhinitis was *Aspergillus fumigatus*. Exposure time was over 5 years in 63% of the patients. Association between the IgE sensitization to molds and exposure level was statistically significant (Fisher's exact test, $p = 0.046$).

Conclusion: This is the first clinically investigated series on occupational rhinitis in relation to a moldy environment. Based on our findings, we conclude that molds growing in conjunction with moisture damages can induce occupational rhinitis. IgE-mediated allergy to molds was not common. Atopy and significant exposure level increased IgE sensitization to molds. zri00508

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Key words: Dampness, fungi, indoor air, moisture, mold, nasal provocation test, occupational, rhinitis, sensitization, upper respiratory symptoms

Building-related moisture and mold damage constitute significant indoor air problems in a growing number of countries.¹ According to Finnish studies, moisture problems have been estimated to occur in over 50% of, e.g., schools and day care centers.^{2,3}

Upper respiratory tract problems are the most commonly reported work-related symptoms in association with dampness in workplaces.⁴ These include nasal congestion, sneezing, and runny or itchy nose. When these symptoms occur episodically and are work related, the condition can be defined as occupational rhinitis.⁵ In addition to mucosal symptoms and respiratory symptoms, a variety of general symptoms such as fatigue and headache are often reported.⁶

The causal relationship between indoor air problems and the symptoms is often difficult to verify. In addition to microbes and spores, agents such as toxins, volatile organic compounds, and emissions from damp building materials are present in the complex exposure situation.⁷ Various other factors, physical (ventilation, temperature, and humidity) as well as psychosocial and individual factors, may influence the symptoms.¹

The mechanisms behind these symptoms are largely un-

known.⁸ The majority of respiratory symptoms appearing in damp indoor spaces are assumed to be irritative. However, molds may cause IgE-mediated allergic rhinitis as well as asthma.⁹ It has been reported that type I sensitization to molds can be confirmed only in a small minority (<5%) of symptomatic patients exposed to moldy indoor environments.^{10–12}

As far as we know, a patient series with occupational rhinitis induced by molds has not been reported earlier. We describe a series of 56 patients diagnosed with occupational rhinitis. The diagnosis of all patients was confirmed by a positive nasal provocation test (NPT) to molds.

MATERIALS AND METHODS

Patients and Study Design

During 1995–2004, a total of 2200 patients suffering from symptoms associated with working in moisture-damaged and moldy workplaces were examined at the Finnish Institute of Occupational Health. The patients were referred to the Finnish Institute of Occupational Health by ear, nose, and throat (ENT) specialists, by pulmonologists, or by occupational health physicians from all over Finland. In these years, NPT to molds was performed in 369 patients because of suspected occupational rhinitis. Sixty patients (16%) were diagnosed with occupational rhinitis attributable to molds based on verified exposure, work-related nasal symptoms, and clinical investigations including a positive NPT. We wanted to review the patient files of the 60 patients retrospectively. Because 4 patients did not give informed consent, the present study comprises 56 cases. The study was approved by Ethics Committee of the Hospital District of Helsinki and Uusimaa.

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Allergy Evaluation

Skin-prick tests (SPTs) and measurements of specific serum IgE were performed by methods reported previously to assess sensitization to molds.^{13,14} SPTs were performed for available mold allergens (ALK-Abelló A/S, Copenhagen, Denmark) with combinations of the mold allergens listed in Table 1. Histamine hydrochloride (10 mg/mL) was used as a positive control. A positive reaction indicating sensitization was defined as a weal diameter of ≥ 3 mm and equal to or greater than one-half of that of the histamine. The mold-specific serum IgE antibodies were determined using the Pharmacia CAP system RAST RIA (Pharmacia, Uppsala, Sweden) until 1996. After that date, IgE values were measured by the UniCAP system (Pharmacia & Upjohn, Uppsala, Sweden). Specific IgE values of >0.35 kU/L were defined as positive. Sensitization to common environmental allergens was tested by SPT with the allergens provided by ALK-Abelló A/S, Copenhagen, Denmark (Table 2).

Atopic history was defined as having earlier infantile eczema or atopic dermatitis, hay fever or other allergic rhinitis, or allergic asthma. Atopy was defined as having atopic history or a positive result to one or more common environmental allergen in the SPT.

Table 1 Mold allergens used in the skin-prick tests

<i>Acremonium kiliense</i>
<i>Aspergillus fumigatus</i>
<i>Aspergillus versicolor</i>
<i>Aspergillus niger</i>
<i>Cladosporium cladosporioides</i>
<i>Cladosporium herbarum</i>
<i>Neurospora sitophila</i>
<i>Geotrichum candidum</i>
<i>Penicillium brevicompactum</i>
<i>Rhodotorula rubra</i>
<i>Rhodotorula glutinis</i>
<i>Botrytis cinerea</i>
<i>Mucor racemosus</i>
<i>Mucor spinosus</i>
<i>Penicillium expansum</i>
<i>Penicillium notatum</i>
<i>Penicillium brevicompactum</i>
<i>Phoma herbarum</i>
<i>Chaetomium globosum</i>
<i>Fusarium culmorum</i>
<i>Fusarium roseum</i>
<i>Sporobolomyces roseus</i>
<i>Sporobolomyces salmonicolor</i>
<i>Phialophora bubakii</i>
<i>Trichoderma viride</i>
<i>Aureobasidium pullulans</i>
<i>Rhizopus nigricans</i>
<i>Trichosporon pullulans</i>
<i>Ulocladium botrytis</i>

Table 2 Common environmental allergens used in the skin-prick tests

Pollens
Birch
Alder
Timothy
Meadow foxtail
Mugwort
Dandelion
Epithelia
Horse
Dog
Cat
Cow
Dust mites
<i>Dermatophagoides farinae</i>
<i>Dermatophagoides pteronyssinus</i>
Molds
<i>Alternaria alternata</i>
<i>Cladosporium herbarum</i>
Latex

Nasal Provocation Tests

Before NPT, other causes for rhinitis were excluded. The NPT was performed as described previously.^{15,16} Allergens were applied on the topical surface of the inferior turbinate by applying a small piece of neurosurgical cotton disk saturated with 0.1 mL of the allergen or by dropping 0.1 mL of allergen solution from a syringe with a metal suction tip. The degree of rhinorrhea and nasal blockage was evaluated immediately before and 15 and 30 minutes after the provocation. Anterior rhinoscopy was done by an ENT specialist and changes in the rhinorrhea and blockage from both nostrils were scored from 0 (dry mucosa or mucosa lining only the bony turbinate) to 3 points (dripping mucus or swelling of the mucosa obstructing nasal cavity).¹⁵ The NPT was regarded as positive if the total sum of the score points changed by at least 4 points for both nostrils within 30 minutes and if the placebo test gave a negative result.

Acoustic rhinometry was used to support the evaluation of the test. The measurement was performed according to a standardized procedure.¹⁷ Volume minimum cross-sectional area percent (MCA%), which is the mean of the percentile changes of nasal volumes and MCAs, was used as a parameter describing the change in the nasal cavity.¹⁸ A decrease of at least 15% was regarded as relevant.¹⁸

The allergens used in the NPTs were mainly water-based commercial fungal products that were available at the time in question.¹⁹ The majority of the tests were performed with water-based extracts of *Aspergillus fumigatus*, *Cladosporium cladosporioides*, and *Acremonium kiliense* (from ALK-Abelló; used at 1:1000 or 1:100 w/v). Between the years of 2000 and 2004, only these three fungal allergens were commercially available. Since the end of 2003, the *A. fumigatus* extract (10,000 BU/mL) manufactured by Allergopharma (Reinbek, Germany) was used. In the 1990s, SPT extracts containing glycerol were used

infrequently in NPTs (*Penicillium brevicompactum*, *Rhodotorula rubra*, and *Cladosporium herbarum*). Depending on the fungal allergen extract, the corresponding diluent was used for a placebo test.

The choice of a microbial extract for the NPT was made among the mold species that were found in the microbial samples taken at the workplace. In addition, if IgE sensitization to some mold was detected, then that fungal allergen was used in the NPT if available.

Exposure Evaluation

An experienced indoor air researcher evaluated the workers' exposure to fungi and bacteria by assessing all of the exposure data in the patient case records. Documents usually included description of the moisture or mold damage in the building and, to a varying degree, microbial measurements. Information was available mostly from material samples.

The period of exposure time was assessed based on the beginning date of the employment in the moisture-damaged building, the point of possible water damage in the workplace, and the dates of the reported damages. The duration of exposure was estimated as (1) <1 year, (2) 1–5 years, (3) 6–9 years, or (4) ≥10 years.

The exposure level was classified by several work-environmental factors:

Category 1, no evidence of mold exposure. Evidence of exposure to microbes was not adequate or reliable. Investigations of moisture and mold damages or indoor air were not performed, reports of them did not exist in the patient files, or exposure data were not associated with the patient's working area.

Category 2, weak mold exposure. An adequate and reliable description of mold damage was reported. A single, small mold damage of <0.5 m² was found in the patient's workspace, or limited mold damage (<1 m²) was detected in the patient's work environment near the patient's permanent workspace.

Category 3, moderate mold exposure. An adequate and reliable description of mold damage, limited number and area of damage (<1 m²), and the total viable concentrations of airborne fungi under 100 CFU/m³ and actinobacteria under 10 CFU/m³. Fungal species requiring a high water activity were not dominant in environmental samples.

Category 4, significant mold exposure. An adequate and reliable description of the extended mold damage (>1 m²) was reported, or total viable concentrations of airborne fungi were over 100 CFU/m³ or the level of airborne actinobacteria was over 10 CFU/m³ or fungal species requiring a high water activity were dominant in environmental samples. This category usually included extended moisture and mold damage, e.g., in the base floor.

Statistical Analysis

Logistic regression analysis was used while examining the association between atopy and IgE sensitization. OR with 95% confidential limits is presented. Other proportional data were compared by Fisher's exact test. The significance level was set

at 0.05. The analyses were performed with SAS 9.1 (SAS Institute, Inc., Cary, NC).²⁰

RESULTS

Patient Characteristics and Symptoms

The mean age of the 56 patients with occupational rhinitis was 43.7 (SD ± 9.5) years. Nearly 90% of them were women (Table 3). Besides symptoms of rhinitis (runny nose, nasal

Table 3 Clinical characteristics of the patients with occupational rhinitis

Subjects (n)	56
Mean age (yr ± SD)	43.7 ± 9.5
Gender	
Female (n [%])	50 (89.3)
Male (n [%])	6 (10.7)
Smoking status (n [%])	
Current smoker	13 (23.3)
Ex-smoker	2 (3.6)
Never smoker	41 (73.2)
Type of workplace (n [%])	
Office	14 (25.0)
Hospital, health clinic or similar	15 (26.8)
School, college	9 (16.1)
Day care center, kindergarten	6 (10.7)
Kitchen	4 (7.1)
Laboratory	2 (3.6)
Production plant	1 (1.8)
Others	5 (8.9)
Level of exposure (n [%])	
Weak	3 (5.4)
Moderate	16 (28.6)
Significant	29 (51.8)
Not classifiable	8 (14.3)
Indicators of atopy	
Atopic history (n [%])	21 (37.5)
Positive SPT to common environmental allergens (n/n _p [%])	20/53 (37.7)*
Elevated serum IgE (>110 kU/L; n/n _p [%])	17/54 (31.5)#
IgE sensitization to molds	
Positive SPT to molds (n [%])	12 (21.4)
Elevated serum IgE to molds (n/n _p [%])	8/34 (23.5)§
Either positive SPT or elevated serum IgE to molds (n [%])	13 (23.3)

*SPT to common environmental allergens was performed in 53 of the patients.

#Total serum IgE was measured in 54 of the patients.

§Serum IgE to molds was measured in 34 of the patients.

n_p = The number of performed tests; SPT = skin-prick test.

congestion, or sneezing), the majority of the patients (75%) also had lower respiratory symptoms (cough, dyspnea, or wheezing; Table 4).

Exposure

All patients had been exposed to molds according to their work history. In most cases, the exposure had taken place in schools, hospitals, day care centers, and various office environments (Table 3). Correspondingly, their occupations included teachers, nurses, cleaners, and office workers. The level of exposure was evaluated to be significant or moderate for 80% of the patients (Table 3). The duration of exposure exceeded 5 years in 63% of the patients.

Atopy

Almost 38% of the patients had a history of atopy. SPT to one or more common environmental allergens was positive in 37.7%, and serum IgE was elevated in 31.5% of the patients (Table 3).

Table 4 The prevalence of symptoms, respiratory infections, and asthma

Symptom/Disease	Patients with Occupational Rhinitis (n = 56; n [%])
Upper respiratory symptoms	
Rhinorrhea	51 (91.1)
Nasal congestion	45 (80.4)
Sneezing	18 (32.1)
Either rhinorrhea, nasal congestion, or sneezing	56 (100.0)
Hoarseness	35 (62.5)
Lower respiratory symptoms	
Cough	33 (58.9)
Dyspnea	23 (41.1)
Wheezing	5 (8.9)
Either cough, dyspnea, or wheezing	42 (75.0)
Other symptoms	
Eye irritation	39 (69.5)
Dermal symptoms	9 (16.1)
Periodic fever	16 (28.6)
Fatigue	27 (48.2)
Headache	18 (32.1)
Vertigo	1 (1.8)
Nausea	3 (5.4)
Arthralgia	6 (10.7)
Respiratory infections	
Recurrent respiratory infections	26 (46.4)
Recurrent sinusitis	22 (39.2)
Sporadic sinusitis (less than four)	8 (14.3)
Physician-diagnosed asthma	15 (26.8)

Specific Sensitization to Molds

SPT to molds was performed in all 56 patients, 12 (21.4%) of whom displayed a positive allergic reaction to one or more of the tested molds. IgE antibodies in sera were measured in 34 patients, of whom 8 (23.5%) showed sensitization to molds. Thus, IgE sensitization, detected either by SPT or serum IgE, was found in 23.3% (13 of 56) of the patients (Table 3). Eleven of these 13 patients were atopic. Atopy increased significantly the risk of sensitization to molds (OR, 10.3 [95% CI, 2.0–52.5]). Type I sensitization specifically to the same mold, which the NPT was performed with, was examined in 55 patients and was detected in 12 of them (21.8%).

In patients with significant, moderate, or weak exposure, the IgE sensitization to molds occurred in 7 of 29, 1 of 16, and 2 of 3 patients, respectively. In 8 patients, the level of exposure was not classifiable. IgE sensitization to molds and the category of exposure were correlated at a statistically significant level ($p = 0.046$).

Nasal Provocation Tests

Altogether, 29 patients had a positive NPT to *A. fumigatus* and 16 patients had a positive NPT to *C. cladosporioides* (Table 5). The nasal responses (the change in volume MCA%) in acoustic rhinometry were compatible with the changes in nasal score points in 33% of the patients (17 of 51); in 5 patients, acoustic rhinometry was not available.

DISCUSSION

There are no data on the causation of occupational rhinitis by specific molds growing in moisture-damaged buildings. Since 2001, three systematic reviews have been published assessing the scientific evidence of the associations of health effects and exposure to moisture and mold in buildings.^{1,21,22} The conclusions of all three are converging: dampness and molds in buildings are associated with adverse respiratory symptoms. According to the review by the Institute of Medicine, there is sufficient evidence of an association with cough, wheezing, exacerbation of asthma, and upper respiratory tract symptoms.¹ In the recent meta-analyses of 33 original studies, building dampness and mold were associated with ~30–50% increases in a variety of respiratory and asthma-related health

Table 5 The performed nasal provocation tests (NPT)

	No. of Positive NPT (n = 56)
<i>Aspergillus fumigatus</i>	29*
<i>Cladosporium cladosporioides</i>	14
<i>Acremonium kiliense</i>	6#
<i>Penicillium brevicompactum</i>	4
<i>Sporobolomyces roseus</i>	2
<i>Cladosporium herbarum</i>	1

*Two patients also had a positive NPT to *C. cladosporioides*.
#One patient also had a positive NPT to *Rhodotorula rubra*.

outcomes.²³ Causation of occupational rhinitis has not been evaluated as a separate health outcome. This may be because of a lack of publications, as well as a lack of international recommendations on the diagnostics of occupational rhinitis caused by moisture and mold.

This study presents for the first time a patient series with occupational rhinitis induced by molds. Our diagnoses were based on verified exposure, work-related nasal symptoms, and clinical investigations including a positive NPT. Limitations in exposure assessment and difficulties in defining specific causative agents have constituted the major flaws of previous studies concerning the relationship between indoor air dampness and molds and health effects.^{1,24} One of the strengths of our study is that the exposure to molds was verified in a detailed assessment. All of our patients had rhinitis symptoms that were assessed to be compatible with occupational rhinitis by an ENT specialist. We also excluded other factors causing rhinitis, such as chronic sinusitis. Finally, we confirmed the diagnosis by a positive NPT. The majority of positive NPTs were obtained with the *A. fumigatus* extract. The use of this extract was reasonable because *Aspergillus* represents a dominant microbe in mold-damaged buildings²⁵ and it is known to share epitopes with other *Aspergillus* species as well as other moisture microbes.^{19,25,26}

The NPT is considered the golden standard in proving causality between occupational exposure and rhinitic symptoms.²⁷ This applies to many well-defined sensitizers for which reliable test materials are available but with respect to moisture microbes, the issue may be uncertain. The use of microbe extracts is hampered by extracts not being standardized and extracts being available for just a few microbes.²⁸ In line with this, the specificity of some of our diagnoses is to some extent unclear, because the NPT extracts used were not uniformly the same as the microbe to which IgE antibody was demonstrated. In workplaces with severe moisture damages, a vast number of different microbial species may be present at various times.^{1,8} Besides microbial spores and fragments, the exposure involves microbial metabolites and other possible compounds in indoor air.¹ The extracts do not reflect the complex exposure situation at the workplace; they contain a small amount of proteins and carbohydrates; they do not contain toxins or spores.²⁸ Moreover, air and material sampling made at one point of time does not necessarily reflect species or amounts of microbes present over a period of time in a moisture-damaged environment.⁸ Thus, there may be multiple reasons for false negative NPTs. Furthermore, NPTs detect immediate, IgE-mediated reactions, but late reactions are not practicable to assess. Because our material indicates the involvement of other mechanisms, the NPT is probably not the method of choice to find cases not induced by IgE antibodies. By comparison with serial peak flow measurements in the diagnostics of occupational asthma, there are, so far, no methods that allow us to follow nasal reactions in the diagnostics of occupational rhinitis.

In the U.S. general population, Gergen *et al.* found 3.6% sensitivity to fungi.²⁹ The prevalence of mold sensitization in association with indoor air exposure has been reported to be ~5%.¹⁰⁻¹² IgE sensitization to fungi has been shown to be associated with building-related symptoms in individuals working in damp and moldy buildings.³⁰ The prevalence of IgE positivity to molds was 23% in our patients with occupa-

tional rhinitis, and, interestingly, almost all of the patients with IgE positivity to molds had atopic tendencies. This is compatible with the suggestion that IgE sensitization to molds may occur in atopic individuals as part of polysensitization.^{25,31}

The mechanisms behind symptoms related to moldy environments are poorly understood. It is probable that several mechanisms are involved because the observed symptoms are so diverse. It has been accepted that molds can be triggers of respiratory symptoms in allergic rhinitis and asthma in atopic individuals.^{9,31,32} One-third of our patients were atopic. Our results indicate that indoor air molds may induce rhinitis not only in atopic subjects but also in nonatopic subjects, and that both IgE- and non-IgE-mediated mechanisms are involved.

Previous reports suggest that upper respiratory symptoms are nonspecific in the majority of symptomatic occupants.⁷ The specific cause of work-related rhinitis is difficult to identify in a damp and moldy work environment. We could show a specific cause in 16% (60 of 369 patients) of the patients examined for occupational rhinitis. Thus, there is an obvious need for the development of diagnostic methods for nonallergic occupational rhinitis. These should include assessments of nasal reactions as well as inflammatory responses on exposure at the workplace. Moreover, because occupational rhinitis is an important risk factor for developing asthma, there seems to be potential for the prevention of the consequent development of occupational asthma by implementing intervention measures at the rhinitis stage.³³

In conclusion, molds growing in conjunction with moisture damages can induce occupational rhinitis. IgE-mediated allergy to molds was not common, but when diagnosed, it occurred predominantly in atopic subjects. The exposure level was significantly associated with IgE sensitization to molds. Diagnostic methods are warranted especially for nonallergic occupational rhinitis related to moldy environments.

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