Hypersensitivity pneumonitis in a cluster of sawmill workers: a 10-year follow-up of exposure, symptoms, and lung function

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Background: The long-term prognosis of repeated acute episodes of hypersensitivity pneumonitis (HP) is not well described. We report on a 10-year follow-up of a 10-person cluster from a Norwegian sawmill who had all experienced relapsing episodes of HP.
Objectives: To evaluate the health symptoms, work-related sick-leave, and lung function of 10 workers exposed to mold in a Norwegian sawmill.
Methods: Participants were evaluated at baseline and 10 years later at follow-up. A structured interview, measurement of serum IgG antibodies to *Rhizopus microsporus* (*R. microsporus*) antigens, lung function tests, high resolution computed tomography (HRCT) of the chest, and personal measurements of exposure to mold spores and dust were completed for each participant.
Results: At baseline, nearly all workers reported acute episodes of HP more than twice a month. At follow-up, both the frequency and intensity of symptoms had declined. Sick-leave was reduced and gas diffusing capacity improved – paralleling the gradually reduced air levels of mold spores.
Conclusions: In spite of an initially high occurrence of symptoms, long-term clinical and physiological outcome was good. With reduced exposure to mold spores, symptoms declined and lung function was restored.

Keywords: Hypersensitivity pneumonitis, Sawmills, Mold spore exposure, Lung function, HRCT scan, Prognosis

Introduction

Hypersensitivity pneumonitis (HP, also known as extrinsic allergic alveolitis) occurs in workers exposed to organic antigens such as agricultural dusts, bioaerosols, and certain reactive chemical species. Typical clinic presentation of HP includes cough, dyspnea, weight loss, fever, chills, and body aches, resulting from an immunologic reaction to the inhaled substance.[1,2]

Both HP-related symptoms and clinically diagnosed cases of HP have been documented among workers employed in trimming departments of sawmills, with the first reports published in the late 1960s, when conventional outdoor drying of timber in Swedish and Norwegian sawmills was replaced by indoor drying in special kilns.[3–5] During the same period, the sorting and trimming of timber was moved indoors in order to improve the working conditions for sawmill workers. However, inadequate maintenance of kiln-drying could promote growth of thermotolerant and thermophilic fungi in many sawmills and result in the dispersion of mold spores into the air at high concentrations during timber processing, subsequently promoting negative occupational health effects.

The health consequences of repeated acute episodes of HP have not previously been well described. The aim of this study is to evaluate the health symptoms, work-related sick-leave, and lung function of 10 workers exposed to mold in a Norwegian sawmill on a 10-year follow-up. This is the first published longitudinal study on HP among wood trimmers and also the first study including quantitative exposure, and may add new information of the clinical presentation and natural history of HP.

Methods

In this study, the diagnosis of HP was based upon the identification of significant predictors of HP including exposure to a known antigen, positive precipitating

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antibodies to the offending antigen, and recurrent episodes of characteristic symptoms occurring 4–8 hours after exposure.[1]

Subjects

In 2002, 16 sawmill workers, with presumed mold exposure, were referred to our clinic for medical examinations. A total of 12 of the referred employees who worked in the trimming department presented with recurrent episodes of chills, fever, and respiratory symptoms after processing boards with mold growth. Data were collected on these 12 employees in January 2003, and they were later invited to participate in a follow-up examination 10 years after their initial baseline visit. Of the 12 symptomatic workers, 10 agreed to participate. Two declined because they had changed occupation and/or moved away from the area.

Interview and questionnaire

All subjects completed a structured interview at baseline and follow-up. Information on work history, non-work-related exposures to mold, and smoking history was collected. Each participant was asked to report their health symptoms and sick-leave related to HP-symptoms in a questionnaire administered by a physician (Table 1).

IgG antibodies to mold spores

Blood samples for the measurement of IgG antibodies to *Rhizopus microsporus* antigens were collected at a different location on two occasions, 6 months before and 2 months after the initial visit. Antibody levels exceeding 10 relative units compared to healthy subjects were considered elevated.[6]

Lung function measurements

Lung function tests included dynamic spirometry and determination of static lung volumes and gas diffusing capacity. All tests were performed according to the ATS-European Respiratory Society (ERS) task force guidelines using the V_{max} V6200 automated system (SensorMedics, VIASYS Respiratory Care Inc, Yorba Linda, CA, USA).[7] Recorded spirometric variables were forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and FEV_1/FVC. Static lung volume variables were total lung capacity (TLC) and residual volume (RV). Gas diffusing variables were the transfer factor for carbon monoxide (DLCO) and DLCO divided by alveolar volume (DLCO/VA). Lung function values were expressed as absolute values and as a percentage of predicted normal values. Values recommended by the ERS were used as reference.[8,9] Fraction of exhaled nitric oxide (FeNO) was measured according to the ATS/ERS criteria, using the NIOX (Aerocrine, Solna, Sweden).[10] This device provides FeNO measurements at 50 ml/second exhalation flow rate, expressed in parts per billion (ppb) using an electrochemical sensor. The values published by Olin *et al.* were used as a reference.[11]

Table 1 Symptoms and sick-leave in 10 wood trimmers

	Baseline	Follow-up
Febrile attacks	10	5
Chills	10	5
Fever attacks	4	2
Upper airways symptoms	5*	1
Nasal obstruction	4	
Nasal discharge	2	
Sore throat	4	1
Lower airways symptoms	5*	0
Cough	1	
Chest tightness	3	
Shortness of breath	2	
Wheezing	2	
HP-episodes: >20	7	0
HP-episodes: 6–20	2	0
HP-episodes: 3–5	0	4
HP-episodes: 1–2	1	1
HP-episodes: none	0	5
Sick-leave medical doctor	2	0
Sick-leave self administrated	2	0

HP: hypersensitivity pneumonitis.
* The same five workers.

Acquisition and review of HRCT images

Thin-section computed tomography (CT) images were obtained with a HiSpeed T/i scanner (GE Medical Systems, Milwaukee, WI, USA) at 140 kV and 200 mA, and a 1-second scanning time with 1-mm section thickness at 10 mm intervals. Images were reconstructed with a high-spatial-frequency (bone) algorithm, and lungs were examined from the apex to the base. Six supplementary expiratory scans were obtained for each subject. In one subject, supplementary images were obtained in the prone position. Readings were performed by a chest radiologist who had no knowledge of the lung function test results. As the patients' symptoms were considered to be mild, no routine high resolution computed tomography (HRCT) thorax was repeated at the 10-year follow-up.

Exposure

All timber processed in the sawmill was Norwegian spruce (*Picea abies*), and all the study participants were considered to be exposed to fungal spores and wood dust at approximately the same intensity. The foreman had experienced chills and fever after working in mold-contaminated areas.

Seven series of measurements of air-borne mold spores and wood dust were obtained in 2001, 2002, 2004, 2006, 2007, and 2009, in total 27 stationary samples and 52 personal samples (Table 3). Samples were collected on 25-mm-diameter polycarbonate filters with a pore size of 0.8 μm in standard aerosol cassettes made of graphite-filled polypropylene using battery powered pumps at a flow rate of 2 l min^{-1}. The sampling time was 2–3 hours during working

Table 2 Lung function at baseline and at 10-year follow-up

	Sawmill workers (n=10)		
	Median (range)		
	Baseline	Follow-up	*P*-value
TLC (l)	7.1 (5.7–9.1)	7.1 (6.0–9.4)	0.11
TLC (% predicted)	93 (84–119)	98 (78–123)	0.17
FVC (l)	5.6 (4.5–6.7)	5.0 (3.6–6.1)	0.005
FVC (% predicted)	109 (92–130)	98 (83–123)	0.007
FEV_1 (l)	4.5 (3.1–5.2)	4.1 (2.6–4.5)	0.005
FEV_1 (% predicted)	109 (86–127)	99 (75–128)	0.02
FEV_1/FVC (%)	81 (71–87)	81 (70–87)	0.55
DLCO (SI-units)	9.2 (7.2–12.5)	10.5 (8.6–11.7)	0.03
DLCO (% predicted)	78 (71–112)	93 (74–111)	0.03
DLCO/VA (SI-units)	1.27 (0.99–1.63)	1.58 (1.02–1.97)	0.02
DLCO/VA (% predicted)	80 (68–108)	104 (77–138)	0.007
Exhaled NO (ppb)	16 (6–43)	12 (5–26)	0.09

Paired samples, non-parametric test (Wilcoxon signed-rank test). TLC: total lung capacity; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; DLCO: transfer factor for carbon monoxide; VA: alveolar volume; NO: nitric oxide.

hours in the trimming department. The number of mold spores was counted by scanning electron microscopy.[12] The levels of wood dust were assessed by gravimetry.

Statistical analyses

All lung function variables showed normal distribution. However, due to the small sample size (n=10), we used a non-parametric test (Wilcoxon signed-rank test) for comparing values at baseline and 10-year follow-up (paired samples).

As the exposure data were highly skewed, and close to log normally distributed, the air measurements were described by arithmetic means as well as geometric means and geometric standard deviations. The geometric means and geometric standard deviations were obtained by the anti-log of the arithmetic means and the standard deviations of log-transformed data. Only the arithmetic means of the dust exposures are shown because of numerous data below the detection limit and generally low dust levels. Statistical tests of spore exposures levels in different years were performed on the log-transformed data using the univariate general linear model procedure of IBM SPSS Statistics version 20.

Table 3 Exposure levels of fungal spores and total dust in wood trimmers

			Fungal spores, $10^6/m^3$		Dust, mg/m^3
Year	Month	*N*	AM	GM (GSD)	AM
2001	January	1	9.8	9.8	3.4
2002	January	13	4.8	1.2 (7.8)	1.0
2002	June	11	0.53	0.061 (8.9)	0.020
2004	May	15	0.080	0.18 (13)	0.087
2006	March	3	0.62	0.46 (2.7)	0.018
2007	May	18	0.20	0.027 (8.1)	0.14
2009	October	18	0.037	0.019 (3.3)	0.091

AM: arithmetic mean; GM: geometric mean; GSD: geometric standard deviation.

Results

Subjects

All 10 subjects were men, aged 25–55 (mean 39) at the initial examination. Nine were employed as wood trimmers and one was a foreman. Duration of employment in the trimming department at baseline ranged 2–12 (mean 7) years. At the 10-year follow-up, 6 of the 10 subjects still worked as wood trimmers, 3 had been relocated to another department in the sawmill, and 1 had retired. Three of the participants had previously been employed in other types of work (slaughterhouse, poultry plant, and fish industry), while seven had worked exclusively in the sawmill. Six subjects were current smokers, and four were never smokers.

Symptoms

The most common symptoms reported by the participants were fever and chills, typically occurring approximately 4–8 hours after exposure to the antigen and generally resolved within a few days (Table 1). At baseline, 7 out of 10 subjects reported symptoms more than twice a month during all seasons, with slightly enhanced occurrence of symptoms in the autumn. At follow-up, five of the wood trimmers still reported HP-episodes, although symptoms were mild and occurred between one and five times per year and exclusively when they were involved in processing wood boards with mold growth. Sick-leave related to HP-symptoms was low, at baseline 0–20 (mean 3.5) days per year and 0 day at follow-up (Table 1). None of the subjects showed weight loss. BMI at baseline ranged from 23 to 31 (mean 26) kg/m^2 and from 21 to 37 (mean 28) kg/m^2 at follow-up. All subjects were in general good physical health; none showed dyspnea on exertion, either at baseline or at follow-up.

IgG antibodies to mold spores

IgG antibody levels to *R. microsporus* >10 relative units were found in 7 of the 10 subjects, for 3 of them on both times of measurements. The individual levels did not divert much.

Lung function

Table 2 presents lung function and FeNO at baseline and follow-up. Lung function was well-preserved at baseline and at follow-up, with median lung volumes about 100% of predicted and median gas diffusing capacity around 80% of predicted for all participants. At follow-up, there was a significant decrease in FVC and FEV_1, but the ratio between the two (FEV_1/FVC) and TLC remained unchanged. There was a significant increase in median percentage of predicted DLCO 78 (71–112) between baseline and follow-up 93 (74–111) ($P=0.03$). This finding was strengthened when DLCO was adjusted for alveolar volume ($P=0.007$). At the baseline examination, 6 of the 10 subjects had DLCO below 80% of predicted, commonly used as a cut-off value for normal versus pathological lung function because it corresponds to the lower 5th percentile for the recommended summary equation.[9] At follow-up, five of the six subjects had increased their DLCO values to 88–97% of the predicted normal values.

Exhaled NO levels were within the normal range and did not change significantly between baseline and follow-up.[11]

HRCT thorax

Air trapping on expiratory scans was observed for five subjects. One subject had findings consistent with subacute or chronic HP. Another presented with a 13 mm nodule at the base of the left lung, which had disappeared at 6-month follow-up examination. Two subjects presented other HRCT findings suggestive of airways disease. Such findings are frequently observed in smokers and not necessarily related to exposure to mold spores.

Exposure

Analysis of variance (ANOVA) showed that the personal measurements and stationary measurements of mold spores and dust collected on the same day did not differ significantly ($P>0.4$). Therefore, all measurements were regarded as estimates of personal exposure (Table 3). At baseline, the exposure levels of mold spores in the trimming department were higher in the winter than in the summer (arithmetic means 4.8×10^6 and 5.3×10^5 spores/m^3, respectively). At follow-up, the mold spore exposure levels were gradually reduced by a factor of 100 from 5×10^6 to 4×10^4 spores/m^3, showing a statistically significant decrease (ANOVA $P<0.001$). At baseline measurement, the exposure levels for the wood trimmers who sorted timber were significantly higher than for those who packed the sorted timber ($P=0.03$), but due to job rotation this likely did not result in meaningful exposure differences between the wood trimmers. Dust levels dropped from 1 to approximately 0.1 mg/m^3 between baseline and follow-up. Combined measurements from 2007 and 2009 had a geometric means of 2.3×10^4 spores/m^3 and a geometric standard deviations of 5.4 ($N=36$). The 99 percentile of this distribution was 1.4×10^6 spores/m^3.

At baseline, nine of the workers reported that they occasionally wore FFP2 or FFP3 filter masks. During 2003–2006, airflow respirators were used by most of the workers on the conveyor belt, and at follow-up, all wood trimmers reported occasionally using FFP2 filter masks.

Discussion

This study found that among 10 sawmill workers, the occurrence of acute HP-symptoms and the number of days of sick-leave were gradually reduced over a 10-year period. This decrease corresponds with a measured diminuation of occupational exposure levels to mold spores for the employees. None of the participants presented with severe HP-symptoms and returned to good health without respiratory disability. These findings are in line with other studies, which have found that HP-symptoms among wood trimmers are frequently reported,[5,13] but cases of severe HP are rare.[13] To our knowledge, this is the first study that included quantitative assessment of the suspected antigen/allergen during follow-up.

An alternative hypothesis to explain the respiratory symptoms experienced by the employees would be that they had experienced organic toxic dust syndrome (ODTS) rather than acute episodes of HP. However, we find this hypothesis to be less likely because 7 of 10 workers had precipitating antibodies (IgG) against *R. microsporus*, supporting a HP diagnosis over ODTS.[14] Furthermore, DLCO was low in six subjects at baseline and improved over time, and all subjects reported experiencing fewer symptomatic episodes over time. One subject had HRCT changes indicating subacute or chronic HP, whereas five subjects had HRCT changes suggestive of air trapping. In ODTS, pulmonary function and chest radiograph are usually normal.[14] Accordingly, the DLCO and HRCT findings in our subjects seem to be in favor of HP rather than ODTS, and an overall clinical judgment indicates that HP is a more probable diagnosis than ODTS. There were no indications for bronchoscopy and therefore findings from bronchoalveolar lavage or biopsies are unavailable.

It has been well established that the incidence of HP can be reduced by diminishing exposure to provocative antigens.[2,15–18] In the present sawmill, an improved drying process in the new kiln built in 2008 helped to reduce occupational mold exposure. Additionally, the duration of outdoor storage of sawn timber before drying was reduced, resulting in less mold growth on the wood. These two process modifications were probably the main factors contributing to the reduced occurrence and intensity of HP-symptoms at follow-up. The use of respirators when carrying out high exposure tasks such as dust cleaning and removing dust from sensors in the trimming department by compressed air also likely reduced exposure to mold spores.

A typical value for spore concentrations in moldy buildings is 10^3 spores/m^3 air.[19,20] In Norwegian sawmills during the 1980s, spore counts as high as 10^7 spores/m^3 air were recorded.[21] In our series, sawmill workers were exposed to spore concentrations of up to 2.0×10^7 spores/m^3 air at baseline and up to 1.8×10^5 spores/m^3 air at follow-up. Because of major improvements to prevent mold exposure among sawmill workers since the 1980s, present sawmill workers are very seldom exposed to such high levels of mold spores. In spite of substantial reductions in exposure level, of the six participants still employed in the sawmill trimming department, five reported experiencing 1–5 HP-episodes per year at follow-up. The upper level of expected exposures based on air measurements in 2007 and 2009 was estimated to be approximately 10^6 spores/m^3, similar to or lower than exposure levels associated with attacks in HP patients.[22] Information about exposure levels associated with ODTS is more limited, but in a small Swedish study, farmers diagnosed with ODTS experienced febrile attacks after approximately 10 times higher exposure levels than farmers diagnosed with HP.[23] These observations further support that the episodes revealed in this study are due to HP.

In spite of their long-term history of HP, the sawmill workers demonstrated well-preserved lung function both at baseline and at the 10-year follow-up. Baseline ventilatory function was about 100% of predicted at both examinations while gas diffusing capacity was slightly below the lower limit of normal at baseline and normalized at follow-up. In fact, gas diffusing capacity increased significantly over the 10-year observation period.

One limitation of this study is the small sample size, which imposes restrictions on statistical analyses, and results should be interpreted with caution. For this reason, we choose to attach clinical significance only to statistically significant differences that are physiologically plausible and could be hypothesized *a priori*. Hence, we believe that the observed increase in the predicted DLCO% is of clinical relevance because it parallels both an improvement in symptoms and a reduction in mold exposure. The workers' smoking habits remained unchanged throughout the 10-year period, and the increase in DLCO is therefore not explained by a reduction in exposure to tobacco smoke, but is more likely due to reduction in exposure to mold spores, causing less inflammation interfering with gas exchange. Statistical analyses showed a significant decline in spirometric lung volumes, but without a concomitant change in TLC. We cannot offer any physiological explanation about why spirometric volumes should decrease while static volumes measured by whole body plethysmograhy remained unchanged. However, because the ratio FVC/FEV$_1$ also remained unchanged, it may be derived that there is no trend toward either an obstructive or a restrictive ventilatory pattern. Thus, we think it is fair to suggest that the decreases in spirometric volumes, even though statistically significant, have no apparent clinical implications.

Exhaled NO levels were within the predicted normal range and did not change between baseline and follow-up. However, smoking is known to down-regulate the NO synthases, resulting in substantially lower FeNO values in smokers. Six of the sawmill workers were current smokers, and their smoking habits remained unchanged throughout the 10-year observation period. The usefulness of measuring FeNO as a marker of airway inflammation associated with occupational exposure in smokers is limited and only modest importance should be attached to the finding of normal FeNO levels in our small cluster of sawmill workers because it includes a number of smokers.

Studies have shown that the majority of persons with HP will experience near total recovery of lung function when avoiding exposure to antigens.[16,24,25] This observation seems to be valid irrespective of the agents causing HP. For instance, in acute cases of HP among farmers – also often caused by mold exposure, most of the recovery takes place during the first months, although in some cases it may also take up to several years.[23,25] In general, PaO$_2$ improves more rapidly than FVC, while a recovery in gas transfer seems to take the longest time.[24]

At baseline, HRCT findings were modest in 9 of the 10 sawmill workers. Only one subject had pathological findings consistent with subacute or chronic HP. Signs of air trapping and other minor manifestations of airways disease were observed in seven subjects. At follow-up, there was no reason to believe that the HRCT manifestations had progressed, rather the contrary, because both symptoms and gas diffusing capacity had improved. For this reason, we did not find it necessary to carry out a second CT scan and expose the subjects to additional radiation. As only minor changes were detected on HRCT in spite of the subjects' long history of relapsing respiratory symptoms, this may suggest a non-aggressive and reversible type of inflammation (alveolitis), a hypothesis supported by the subjects' well-preserved lung function.

In cases of HP in farmers, relocation in order to avoid antigen exposure often poses problems due to financial and emotional consequences of leaving the farm environment.[26] Similar problems were encountered by the wood trimmers in our survey. Finding a new job in the area nearby was difficult, and some of the workers had previously experienced periods of unemployment. Consequently, the wood trimmers stayed in their jobs in spite of the exposure to mold spores and the discomfort of experiencing relapsing HP-symptoms. Also studies of HP in farmers have found that the subjects generally recover with only minor, if any functional abnormalities, and very few progress to an advanced, debilitated state.[16,24,25] An impaired pulmonary gas transfer and a tendency toward airway obstruction over time are the most common defects reported in exposed farmers.[27]

This study has several strengths and limitations. The homogeneous and well-defined study group, precise and comprehensive measurements of exposure, and longitudinal design are all strengths. The small sample size and subsequent restrictions on statistical analyses and interpretations are the major limitations. The lack of diagnostic HRCT findings in our series, including ground-glass opacification, might be limitations; however, the HRCT scans can be normal in acute cases of HP due to the fleeting nature of the radiographic opacities.[28] Air trapping can also be found in obstructive airway disease.[29]

We conclude that in spite of an initially high occurrence of HP-symptoms, the long-term clinical and physiological outcomes of repeated episodes of HP among wood trimmers seem to be favorable. The HP-symptoms in this cluster of wood trimmers were mild, and no severe cases were observed. As both severity and occurrence of symptoms as well as sick-leave reduced and gas diffusing capacity increased, we hypothesize that the reduced exposure to mold spores likely results in a reduced risk of serious long-term lung function impairment in these workers. However, further studies with long-term follow-up of symptomatic cases are needed to predict prognosis. As HP is a rare but potentially serious disease, alertness is required from the occupational health services at workplaces with increased risk of HP and/or departments of occupational health at regional and university hospitals. In future epidemiological studies on HP, we would recommend a strategy including work site visits with measurements of potentially offending agents, a team work approach including immunological, occupational, and respiratory medical competence, and a longitudinal study design.

Disclaimer statements

Contributors KF conceiving and designing the study, obtaining ethics approval, collecting of data, analyzing of data, interpreting the data, writing the article in whole, revising the article. MBL collecting of data, analyzing of data, interpreting the data, writing the article in part, revising the article. TMA collecting of data, analyzing of data, writing the article in part. WE analyzing of data, interpreting the data, writing the article in part, revising the article. PS collecting of data, analyzing of data. SL conceiving and designing the study, writing the article in part, revising the article. JK conceiving and designing the study, analyzing of data, interpreting the data, writing the article in part, revising the article.

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