Chronic rhinitis in workers at risk of reactive airways dysfunction syndrome due to exposure to chlorine

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Abstract

Background—To assess the frequency of chronic upper airways symptoms and to relate the presence of these symptoms to accidental exposure to chlorine and changes in lower airways symptoms, airway function, and bronchial responsiveness in a cohort of workers at risk of sporadic occupational exposure to high concentrations of chlorine

Methods—Data were collected on symptom assessment, spirometry, and methacholine challenge tests from 211 workers seen twice at a 2 year interval (1992–4).

Results—The proportion of workers reporting chronic rhinitis was 46.9% in 1992 and 42.2% in 1994. Chronic rhinitis reported in 1994 was significantly associated with acute exposure to chlorine (self reports, $p=0.02$; first aid reports, $p=0.001$). In a multivariate logistic regression analysis the presence of reported accidents at the first aid unit (one accident, odds ratio (OR) 3.1, 95% confidence interval (95% CI) 1.3 to 7.5; two or more accidents, OR 6.2, 1.1 to 35.8) and of personal atopy (OR 5.5, 2.2 to 10.8) were significant predictors of chronic rhinitis in 1994. Chronic lower airways symptoms were more frequent in 1994 among workers reporting chronic rhinitis on both assessments than in others ($p=0.03$) and changes in bronchial responsiveness were more pronounced in those with persistent rhinitis ($p=0.09$).

Conclusions—These results suggest that persistent nasal symptoms in workers at risk of reactive airways dysfunction syndrome could be a useful marker of lower respiratory tract abnormalities.

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such irritant exposure on the upper airways. In many case reports of RADS, subjects complained not only of lower respiratory tract symptoms, but also of a burning sensation in the nose and throat.³ Reactive upper airways dysfunction syndrome (RUDS) was recently proposed by Meggs to describe chronic rhinitis after an acute irritant exposure.⁴

Chlorine gas is one of the most common offending agents that can cause RADS, both at the workplace and in domestic use. In epidemiological surveys conducted mainly in pulp and paper mills, occupational hazard due to chlorine may combine chronic exposure to low concentrations with several brief exposures to high concentrations that may cause irritant induced asthma.³ Brooks *et al* have recently proposed the term “not so sudden onset asthma” for the clinical manifestation of irritant induced asthma that is caused by prolonged exposure to a low concentration of an irritant agent and takes longer to evolve.⁵ Studies have shown significant changes in airway calibre in association with past gassing episodes.^{6–8} We recently conducted a cross sectional survey of 239 workers at risk of exposure to chlorine. Repeated acute exposure was associated not only with mild, but significant reduction in expiratory flow rates, but also with an increase in airway responsiveness, as assessed through the methacholine dose-response slope.⁹ Reassessment was performed in the same way after a 2 year interval.

The purpose of the present study was to assess the frequency of chronic upper airways symptoms and to relate the presence of these symptoms to accidental exposure to chlorine and changes in airway function and bronchial responsiveness in this cohort of workers at risk. Our hypotheses were that: (a) the presence of upper airways symptoms should occur more often in those workers experiencing accidental exposure to chlorine; (b) lower airways symptoms should occur more often, and changes in airway function and bronchial responsiveness should be more pronounced, in those workers with persistent rhinitis.

Methods

SUBJECTS AND STUDY DESIGN

All subjects worked in a plant that started operations in 1989. We assessed an initial cohort of 239 out of the 255 workers at risk in the autumn of 1992; of those, 211 workers (88.3%) completed the follow up assessment during the autumn of 1994. The study focused on the relation between acute high level

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Accidental inhalation of gas, fume, or vapour with irritant properties can lead to reactive airways dysfunction syndrome (RADS). Diagnosis criteria for RADS associate a rapid onset of asthma-like symptoms after exposure that persist for at least 3 months with bronchial hyper-responsiveness on methacholine challenge test, in a subject previously free from respiratory complaints.¹ A great deal of attention has been paid to RADS, since this term was first proposed by Brooks and colleagues in 1985.^{2–3} By contrast, little is known about the effects of

exposure, chronic symptoms from upper and lower airways, and changes in airway function and bronchial hyperresponsiveness over the 2 year period. The study protocol was approved by the Hôpital du Sacré-Coeur Ethics Committee and written informed consent was obtained from all participants. Data were collected at the workplace by a trained nurse and two medical technologists.

TESTING PROCEDURES

We administered a French adapted version of the International Union against Tuberculosis and Lung Diseases questionnaire to assess the presence of chronic symptoms, a history of physician diagnosed asthma, personal allergic conditions (eczema, urticaria, and hay fever) and smoking.¹⁰ Questions on upper airways symptoms dealt with the presence of nasal congestion, runny nose, or sneezing; questions on lower airways symptoms looked at the presence of wheeze, symptoms with smoke, shortness of breath, and symptoms on exercise. Exposure to chlorine in workers at risk was assessed in two ways. Firstly, a questionnaire focused on accidental exposure to chlorine (referred to as "puffs"), to evaluate the occurrence of puffs, the number of events per year, and the occurrence and intensity of respiratory symptoms after inhaling puffs (expressed as absent, mild, or considerable). Secondly, data from individual reports of inhalational accidents attributed to chlorine were collected from the first aid unit of the factory. In 1992, the information was collected for the period starting in 1989, when the plant began its operations; in 1994, the information was obtained for the 2 year follow up period.

Pulmonary function tests were carried out at the time of the questionnaires. Spirometric measurements were performed according to the criteria of the American Thoracic Society using a Collins-type spirometer.¹¹ The following measurements were performed and derived: forced expiratory volume in one second (FEV₁), forced vital capacity (FVC). Results were expressed as a percentage of the predicted value. Reference values for spirometry were obtained from Knudson *et al.*¹² Methacholine challenge tests were performed according to a standardised methodology with a Wright nebuliser (Aerosol Medical, Colchester, Essex, England) (output = 0.14 ml.min⁻¹), and methacholine inhaled at tidal volume breathing for two minutes.¹³ An abbreviated method, with a starting concentration of 2 mg.ml⁻¹, was applied in subjects with lung function results within the normal range and no suggestive history of asthma.¹⁴ The test ended at the level of 32 mg.ml⁻¹ if a 20% fall in FEV₁ had not been reached. Challenge tests were performed by medical technologists under the close supervision of the occupational physician. The test was postponed for 2 weeks in subjects with a current acute upper airway infection.

DATA ANALYSIS

Chronic rhinitis was defined by a positive response on the questionnaire to the presence of at least one of the following perennial symp-

toms: nasal congestion, runny nose, or sneezing. At least one positive response to the following questions: "have you ever suffered from asthma?", or "...hay fever?", or "...urticaria?", or "...eczema?" was required to define personal atopy. Several indices of exposure were generated from the two occupational history questionnaires of 1992 and 1994: accident report; occurrence of puffs as reported in the questionnaire and classified according to the occurrence of immediate symptoms (absent, mild, considerable); and number of puffs with mild symptoms. Dose-response curves to methacholine were drawn on a semilogarithmic, non-cumulative scale. Measurable PC₂₀ was interpolated on the individual curve. Two parameters of bronchial responsiveness were considered for analysis: a PC₂₀ ≤ 16 mg.ml⁻¹ (which defined significant bronchial hyperresponsiveness) and the slope of the dose-response curve, which was calculated to study a quantitative, continuous variable for all subjects, as is recommended for population studies.¹⁵

All questionnaire responses and lung function results were coded, verified, and registered in computer files. Analyses were performed with the SPSS/PC+ statistical software package (Chicago, IL, USA). Analyses were conducted in three steps. Firstly, we studied the association between reported chronic rhinitis and exposure to chlorine, with χ^2 analysis, Fisher's exact test, and McNemar test. Secondly, multivariate logistic regression analyses were performed to evaluate the effects of potential risk factors on the presence of chronic rhinitis at the beginning of the survey (1992) and at the follow up assessment (1994) and on the presence of persistent rhinitis (reported chronic rhinitis in 1992 and 1994). For categorical independent variables (accident reports, smoking), simple contrasts were used, where the absence of the characteristic was considered as the reference level. Odds ratios and their 95% confidence intervals (95% CIs) were estimated. Thirdly, analyses of the frequency of lower airway symptoms and the changes in airway function and bronchial responsiveness were accomplished with χ^2 analysis, Fisher's exact test, and Student's *t* test. A *p* value ≤ 0.05 was considered significant.

Results

Table 1 shows the associations between the presence of chronic rhinitis in 1994, the presence of chronic rhinitis in 1992, and exposure to chlorine since the beginning of employment, in the 211 workers who completed the study. Chronic rhinitis was present in 67 subjects and absent in 90 subjects on both assessments. The proportion of subjects reporting chronic rhinitis was 46.9% (n=99) in 1992 and 42.2% (n=89) in 1994 (*p*=0.22, McNemar test). The presence of chronic rhinitis in 1994 was significantly associated with the presence of chronic rhinitis in 1992 (*p*<0.001). Among the 89 subjects who reported chronic rhinitis in 1994, 45 complained of nasal congestion, 63 of runny nose or sneezing, and 19 of both nasal congestion and runny nose or sneezing. Among the 70 workers reporting the

Table 1 Reported chronic rhinitis in 1994, in the 211 workers, and relation to chronic rhinitis in 1992 and cumulated exposure

	Present		Absent
	Nasal congestion, runny nose, or sneezing n=70 n (%)	Nasal congestion, and runny nose or sneezing n=19 n (%)	n=122 n (%)
Rhinitis in 1992:			
Absent	21 (30)	1 (5.2)	90 (73.7)
Present	49 (70)*	18 (94.7)†	32 (26.2)
Accident report to first aid:			
None	52 (74.2)	12 (63.1)	108 (88.5)
One	11 (15.7)	6 (31.5)	12 (9.8)
Two or more	7 (10)‡	1 (5.2)§	2 (1.6)
Ever had a "puff":			
Without symptoms	7 (10)	2 (10.5)	16 (13.1)
With mild symptoms	44 (62.8)	11 (57.9)	90 (73.7)
With considerable symptoms	19 (27.1)¶	6 (31.5)**	16 (13.1)

* $p < 0.001$, χ^2 analysis; † $p < 0.001$, Fisher's exact test; ‡ $p < 0.05$, χ^2 analysis, two rows, two columns, comparing at least one accident report *v* none; § $p < 0.01$, Fisher's exact test, comparing at least one accident report *v* none; ¶ $p = 0.02$, χ^2 analysis, comparing ever had a "puff" with considerable symptoms *v* others; ** $p = 0.05$, Fisher's exact test, comparing ever had a "puff" with considerable symptoms *v* others.

Table 2 Logistic regression analysis with odds ratio (95% CI) for the effects of age, atopy, smoking, and chlorine exposure on the presence of chronic rhinitis in 1994, in 211 workers

Factor	Chronic rhinitis in 1994		Odds ratio	95% CI
	Yes (n=89)	No (n=122)		
Age (mean (SD))	35.5 (5.7)	35.2 (5.8)	1	0.9 to 1.1
Atopy (%)	49.4	17.2	5.5	2.2 to 10.8
Smoking (%):				
Non-smokers	57.3	39.4	1	—
Smokers	13.5	29.5	0.3	0.1 to 0.7
Ex-smokers	29.2	31.1	0.6	0.3 to 1.3
Accident report at first aid (%):				
0	72.1	89.4	1	—
1	19.1	9.8	3.1	1.3 to 7.5
≥2	8.8	1.6	6.2	1.1 to 35.8

Table 3 Chronic bronchial symptoms, bronchial hyperresponsiveness, and airway function in 1992 and 1994 in workers with chronic rhinitis at both assessments compared with other workers

		Workers with chronic rhinitis in 1992 and 1994 (n=67)		Other workers (n=144)
Subjects (n (%)):				
Chronic respiratory symptoms	1992	13 (19.4)		20 (13.9)
	1994	17 (25.4)*		19 (13.2)
PC ₂₀ ≤16 mg.ml ⁻¹	1992	4 (6)		13 (9)
	1994	7 (10.4)		15 (10.4)
Mean (SD):				
Log dose-response slope	1992	0.62 (0.26)		0.61 (0.36)
	1994	0.56 (0.1)†		0.61 (0.36)
FEV ₁ (%predicted)	1992	99.7 (10.8)		98.3 (10.5)
	1994	98.6 (10.4)		97.0 (10.6)
FVC (%predicted)	1992	101.1 (9.9)		100.6 (9.8)
	1994	100.7 (9.9)		100.0 (9.6)

* $p < 0.05$, χ^2 analysis, comparing the frequencies observed in 1994.

† $p = 0.09$, Student *t* test, comparing differences in log dose-response slope between workers reporting chronic rhinitis in 1992 and 1994, and others.

presence of nasal congestion or runny nose or sneezing, chronic rhinitis was significantly associated with exposure to chlorine: accident reported at the first aid unit ($p < 0.05$); questionnaire reported puffs ($p = 0.02$). Cumulated exposure to chlorine was also reported more often in the subgroup of 19 subjects who complained of the presence of nasal congestion together with runny nose or sneezing in 1994: accident reported at the first aid unit ($p < 0.01$); questionnaire reported puffs ($p = 0.05$).

A multivariate logistic regression analysis was carried out with chronic rhinitis reported in 1992 as the dependent variable and accident reports at the first aid unit as the exposure variable (three categories: 0, 1, ≥ 2), control-

ling for age and the potential confounders personal atopy and smoking. Atopy was a significant predictor for the presence of chronic rhinitis in 1992 (OR 4.6, 95% CI 2.4 to 8.9), but not the presence of accident report at the first aid unit (OR 1.1, 95% CI 0.4 to 2.6 for one accident; OR 0.9, 95% CI 0.2 to 4.5 for two or more accidents). Smokers were also less likely to report chronic rhinitis in 1992 (OR 0.4, 95% CI 0.2 to 0.9). The same analysis was carried out for the presence of chronic rhinitis in 1994 (table 2). The presence of at least one accident report at the first aid unit and personal atopy were significant predictors for the presence of chronic rhinitis in 1994. Odds ratios were respectively 3.1 for one accident, 6.2 for two or more accidents, and 5.5 for atopy. Smokers were again less likely to report chronic rhinitis in 1994. When the same analysis was carried out with chronic rhinitis on both assessments ($n = 67$) as the dependent variable, similar results were observed; ORs (95% CI) were respectively 7 (3.5 to 14.3) for atopy, 3.2 (1.3 to 8.4) for one accident report and 1 (0.2 to 5.3) for two or more accident reports at the first aid unit. Similarly, smokers were less likely to report chronic rhinitis (OR 0.3, 95% CI 0.2 to 0.7).

Table 3 shows the frequencies of chronic lower airways symptoms, and of bronchial hyperresponsiveness, and mean values for airway function variables in 1992 and 1994, for subjects who displayed chronic rhinitis on both assessments (67 workers) and others (144 workers). Chronic lower airways symptoms occurred more often in 1994 among those workers reporting the presence of chronic rhinitis on both assessments compared with other workers ($p = 0.03$, χ^2 analysis). By contrast, changes in PC₂₀, mean FEV₁ and mean FVC were comparable among these two subgroups. However, when expressed as log dose-response slope, changes in bronchial responsiveness were marginally more pronounced in the group of 67 workers with persistent rhinitis ($p = 0.09$, Student's *t* test).

Discussion

Two conclusions can be drawn from this 2 year follow up study of 211 workers at risk for accidental acute exposure to chlorine. Firstly, chronic symptoms of rhinitis were often reported and significantly associated with accidental exposure to chlorine, also assessed by means of a questionnaire or through first aid reports. Secondly, chronic lower airways symptoms more often occurred in 1994 among those workers reporting the presence of chronic rhinitis on both assessments. Also, workers with persistent rhinitis showed a tendency to a greater increase in bronchial hyperresponsiveness, as expressed by the slope of the dose-response curve.

Little is known about the long term effects of chlorine gas on upper airways. In animal models, the effects depend on the intensity and duration of exposure. In a study by Wolf *et al*, a 2 year low level (<2.5 ppm) exposure to chlorine of rats and mice led to lesions confined to the nose, including epithelial

hyperplasia, squamous metaplasia, and mucosal inflammation.¹⁶ At higher concentrations (>500 ppm), acute exposure induced persistent lower airways abnormalities, as assessed by Demnati *et al* in a rat model.¹⁷ In humans, numerous case reports of RADS induced by a single acute chlorine inhalation have often mentioned transient upper airways symptoms.² The assessment by Meggs *et al* of 13 workers 5 years after an acute chlorine inhalation suggested persistent upper airways symptoms in all of them¹⁸; nasal biopsies of these subjects showed desquamation of the epithelium, basement membrane thickening, and lymphocytic infiltrates, all pathological features that have also been described in bronchial biopsies performed in patients with RADS.^{19, 20}

Epidemiological studies undertaken in working groups exposed to chronic low levels of chlorine gas and at risk of brief high level irritant exposure focused on the assessment of lower airways abnormalities.^{6-8, 21} For the first time to our knowledge, the presence of chronic rhinitis was related to acute exposure to chlorine, taking into account other personal factors—such as atopy and smoking. Concentrations of chlorine during an acute accidental event were not documented through environmental measurements as discussed earlier.⁹ In this study, as well as in previous studies of workers at risk of acute exposure to chlorine,^{6, 22, 23} self reports, and first aid reports of accidental inhalation have been used as surrogate measures of exposure. The respective effects of atopy and smoking remained comparable in the three analyses carried out with the following dependent variables: chronic rhinitis in 1992; chronic rhinitis in 1994; and persistent rhinitis at both assessments. The effect of exposure was detectable only at the second assessment in 1994; because the plant started its operation in 1989, the initial 3-year working period could seem too short to detect any impact of accidental chlorine inhalation and of prolonged low level exposure. The odds ratios for the presence of chronic rhinitis in 1994 increased with the number of accident reports at the first aid unit (one *v* two or more), suggesting a dose-response relation. Atopy was an independent predictor for chronic rhinitis. It could be argued that atopic subjects are more symptomatically sensitive to chlorine and report a higher frequency of inhalational accidents; however, in this group of workers, atopy was not related to the frequency of accident reports to the first aid unit, or self reported accidents. Smoking affected these findings: chronic rhinitis was less often reported in smokers than in non-smokers, and no association was found between accidental exposure to chlorine and chronic rhinitis in the subgroup of smokers. Reasons for such an effect are unclear; one possible explanation might lie in the concept of healthy smokers,²⁴ people who take up the habit because their airways can be relatively resistant to the effects of smoking; those people less susceptible to tobacco smoke might show a greater tolerance to other irritants as well, at least during the first years of exposure, as might be the case in this

study set up in a plant that started its operation in 1989. Alternatively, perception of upper airways symptoms may differ in smokers.

Relations between upper and lower respiratory symptoms in workers at risk of exposure to chlorine are interesting and remain relatively unexplored. This study shows some association although it is incomplete. The time course of this association warrants exploration. It can indeed be speculated that upper respiratory symptoms of allergy may precede the onset of lower respiratory abnormalities; this hypothesis is also consistent with recently published findings showing the association between atopy and not so sudden onset asthma.⁵ If so, upper respiratory symptoms could be used as a marker of lower respiratory abnormalities. A prospective study of new employees in working populations at risk for RUDS, RADS, and irritant induced asthma (our study included subjects who had already been employed for 3 years at the time of the first assessment) may shed some light on this point.

To confirm these findings, to avoid possible bias induced by questionnaire assessment of chronic rhinitis, and to study the physiopathology of upper airways changes among symptomatic workers, objective testing of upper airways might be considered in further studies: by functional assessments—that is, nasal resistance assessed by rhinomanometry and response to non-specific nasal challenges, or pathological assessments—that is, assessments of mediators and cells by nasal biopsy or nasal scraping. Objective assessment of atopy with allergy skin prick tests to common allergens should be performed.

In summary, our results show that persistent nasal symptoms are associated with acute inhalation accidents in a dose-response manner; and suggest that persistent nasal symptoms are associated with lower respiratory abnormalities. Prospective studies with various means of assessment can better highlight the temporal association between upper and lower respiratory tract abnormalities in high risk workplaces.

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