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- **Short title:** Severity factors of occupational asthma at diagnosis

- **Abbreviations**: OA= occupational asthma, FEV_1= Forced Expiratory Volume in one second, FEF25-75=Forced Expiratory Flow between 25 and 75 of Forced Vital Capacity (FVC), PD_{20} methacholine =provocative dose of methacholine causing a 20% fall in FEV_1, SD = standard deviation, aOR= adjusted Odds ratio, CI= confidence interval, NS= not significant.

- Abstract (225 words)

Background. Severity of occupational asthma at diagnosis is an important prognostic factor. The aim of this study was to determine which factors affect the severity of occupational asthma with latency period at diagnosis.

Methods. The study population consisted of 229 consecutive subjects with occupational asthma with latency period recruited by four occupational health departments and divided into two groups according to the severity of the disease at diagnosis. The moderate-severe (FEV_1 < 70% predicted, or PD_{20} methacholine ≤300 µg; n=101) and mild (FEV_1≥ 70% predicted and PD_{20} methacholine > 300 µg, n=128) groups were compared in terms of clinical and demographic parameters. Multivariate analysis using logistic regressions was performed to examine factors associated with asthma severity.

Results. Duration of symptoms before diagnosis was significantly longer in the moderate-severe group (mean ± SD: 6.3 ± 6.8 years *versus* 3.4 ± 4.4 years, p<0.001). Sex ratio, age, atopy, smoking habits, duration of exposure before symptoms, and molecular weight of the causal agent were not significantly different between the two groups. On multivariate analysis, only duration of symptoms before diagnosis was associated with asthma severity (aOR=1.12, 95% CI 1.05-1.18, p<0.001).

Conclusions. Severity of occupational asthma with latency period at diagnosis was associated with duration of symptoms before diagnosis, but not with the type of causal agent. This finding emphasizes the need for early diagnosis and avoidance of exposure.

-Key words: occupational medicine, asthma, prevention

Introduction

Occupational asthma (OA) is a disease characterized by airway inflammation, variable airflow limitation, and airway hyperresponsiveness due to causes and conditions attributable to a particular environment and not to stimuli encountered outside the workplace (1). It is one of the commonest occupational respiratory diseases in many industrialized countries (2). It has been estimated that 10% to 15% of cases of asthma in adults are associated with occupational factors (3,4).

Severity of OA at diagnosis is an important prognostic factor (5). Factors associated with OA severity might have important clinical and socioeconomic consequences and consequently important implications for management and prevention (6). However, very few studies have described the severity of OA at the time of diagnosis (7).

The aim of this study was to determine which factors affect the severity of OA with latency period at the time of diagnosis.

Materials and Methods

Subjects

We conducted a prospective multicenter study in consecutive patients referred between 2001 and 2004 to four occupational health departments in the Paris area for suspicion of OA. The eligible population consisted of all patients with a confirmed diagnosis of OA with latency period. Cases of OA without latency period (reactive airways dysfunction syndrome (8)), were not included in the study.

According to the proposals of the American College of Chest Physicians (ACCP), the diagnosis of OA (surveillance definition) was based on four criteria (2): (A) diagnosis of asthma based on a compatible history and confirmed by either nonspecific bronchial hyperresponsiveness (provocative dose of methacholine causing a 20% fall in FEV_1 (PD_{20} methacholine) $\leq$ 2000 µg (9)) or a variable airflow limitation, (B) onset of asthma after entering the workplace, (C) association between symptoms of asthma and work, and (D) one or more of the following criteria: (D1) workplace exposure to an agent known to give rise to OA; or (D2) work-related changes in forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF) rate, or (D3) work-related changes in bronchial responsiveness, or (D4) positive response to specific inhalation challenge test.

Patients fitting the ACCP medical case definition [A+B+C+D1+(D2 or D3 or D4)] constituted a sub-sample of the study population (definite OA subgroup). Other subjects were considered as having probable OA (probable OA subgroup).

Investigations

The investigations included:

- an interview by an occupational physician. Information on gender, age, smoking habits, occupation, number of workers in the company, duration of exposure before symptoms and duration of symptoms before diagnosis, and treatment by inhaled corticosteroids at diagnosis, was systematically recorded;
- calculation of a symptom score by means of a standardized questionnaire ob respiratory symptoms over the last fortnight, based on frequency of dyspnea, cough, chest discomfort, wheezing in the chest, and nocturnal awakening, using a five-point scale for each item, ranging from "always" (=1) to "never" (=5). The symptom score was the sum of the 5 items equally weighted, and therefore ranged for 5 to 35 (subjects suffered from important symptoms had then a low score);
- skin-prick tests with the usual airborne allergens (*Dermatophagoides pteronyssinus*, *D. farinae*, cockroach, cat and dog allergens, *Poaceae* and *Betulaceae* pollens, Alternaria) (Allerbio®). Atopy was defined by at least one positive skin-prick test;
- spirometry and methacholine challenge test in the absence of contraindication, or bronchodilator test (in the case of airways obstruction);

In order to confirm the suspected causal allergen involved in OA onset, specific immunologic tests were performed, when appropriate, using quantification of IgE specific antibodies (RAST) or specific skin-prick testing (Allerbio®, Stallergenes® for latex).

Analyses

For the analyses, subjects were classified into two groups according to the severity of OA with latency period:

- mild OA group included workers with FEV_1 ≥70% predicted and PD_{20} methacholine ≥ 300 µg.
- moderate-severe group included workers with FEV_1 <70% predicted or PD_{20} methacholine < 300 µg.

Values for continuous variables were expressed as the mean (standard deviation, sd). Chi-square test and Student t test were used for bivariate analyses. A p-value less than 0.05 was considered statistically significant.

In order to study the influence of time between last exposure and methacholine challenge test on OA severity, we compared patients who had been still exposed to the occupational exposure at the time of functional tests (last exposure less than one week) to patients who ended exposure over one week and over one month.

Multiple logistic regression models were constructed to determine factors associated with severity of OA. Factors investigated were gender, age, smoking habits, atopy, molecular weight of the causal allergen (high *versus* low), duration of exposure before symptoms, duration of symptoms before diagnosis, and symptom score. Missing data for atopy were recoded as no atopy, and missing data for symptom score were recoded as its median. Models limited to subjects with definite OA and subjects with probable OA were also performed.

Statistical Analysis Software (SAS v8.2, SAS institute Inc, Mary, NC, USA) was used for all analyses. This study was approved by the French national committee for data protection (*CNIL: Commission Nationale Informatique et Liberté*).

Results

The study population consisted of 229 patients. General characteristics, symptom score, duration of exposure before symptoms, lung function tests, and PD_{20} methacholine were not significantly different between the four occupational health departments.

Main characteristics of the study population are shown in Table 1 and Table 2. Fifty eight percent (58%) of cases were related to a high molecular weight allergen. The three main causes of OA with latency period were flour, persulfate salts and isocyanates and the three major occupations were bakers and pastry makers, hairdressers and health workers (Table 2).

Forty-four percent (44%) of subjects were classified in the moderate-severe group and 56% in the mild group. The two groups were not significantly different in terms of gender, age, smoking habits, atopy, molecular weight of the suspected causal allergen, and duration of exposure before symptoms (Table 1) and no differences were observed between subjects with definite OA and subjects with probable OA (Table 3).

Duration of symptoms before diagnosis was significantly higher in the moderate-severe group (6.3 years ± 6.8 *versus* 3.4 ± 4.4 years, $p<0.001$). Symptom score was lower and treatment by inhaled corticosteroids at diagnosis was more frequent in this group (Table 1).

No significant difference considering severity parameters (severity group, symptom score, FEV1 and PD20) was observed between subjects who ended occupational exposure over than one month at the time of the functional tests (n=25), ones over than one week patients (less than one month, n=18), and ones less than one week (ie still exposed, n=114; 72 missing data).

On multivariate analysis, factors associated with the risk of having moderate-severe OA were duration of symptoms before diagnosis, treatment by inhaled corticosteroids at diagnosis, and symptom score (Table 4). Logistic models performed in the definite OA and

probable OA subgroups of OA patients gave similar results. Duration of symptoms before diagnosis was significantly associated in both subgroups with the risks of having moderate-severe OA (aOR=1.16 [1.01-1.33] in subjects with definite OA and aOR=1.12 [1.04-1.21] in those with probable OA).

Discussion

In this study, the only parameter clearly related with severity of OA with latency period at diagnosis was the duration of symptoms before diagnosis. No correlation was found with age, duration of exposure before symptoms, molecular weight of the causal allergen, or atopy.

One strength of this study is the large number of subjects. The possibility that cases of OA with latency period in the study population might be nonrepresentative of cases in the general population cannot be ruled out, as a higher severity seems plausible due to the recruitment by hospital departments. However, the distribution of the subjects in terms of age, sex ratio, causal allergens, and jobs is quite similar to that observed in the French ONAP surveillance programme of OA (10).

Two other limitations, concerning the accuracy of the diagnosis of OA and the severity assessments, should also be discussed. Specific inhalation challenge tests, which are often considered as the gold standard for the diagnosis of OA (11,12), were performed in only 8% (n=19) of cases in our study. However, standardized methods are lacking for many occupational agents, and specific inhalation challenge tests are accessible in only a few specialized centres (13-16). Furthermore, they are potentially dangerous and, above all, their sensitivity is far from 100%, with false-negatives corresponding to wrong allergens or insufficient concentrations of test allergens, or a long time interval since end of exposure (15,17). Serial measurements of PEF rates, FEV_1, or nonspecific bronchial hyperresponsiveness have been proposed as a surrogate for specific inhalation challenge tests (18,19). Serial PEF has been demonstrated to have a high sensitivity (from 70 to 93%) and specificity (from 70 to 100%) for the diagnosis of OA, compared with specific inhalation test

or combination tests (12,20-26). Such tests were performed in 21% (n=48) of cases in our study. For the remaining patients, we cannot exclude that some cases considered to be OA cases actually corresponded to work-aggravated asthma. However, in the probable OA subgroup, sensitization to an occupational allergen was demonstrated by positive skin-prick tests or RAST in 31% other patients (n=70). Moreover, the results of multivariate analysis limited to subjects with probable OA did not differ from those of multivariate analysis limited to subjects with definite OA.

The severity assessment is also a matter of debate, as the best way to assess the severity of asthma is still under discussion. Several approaches have been proposed. The UK consensus panel defines severity in terms of the treatment needed to achieve asthma management goals (27). Other methods are based on assessment of respiratory symptoms and lung function measurements (28). Severity scores combining symptom scores and treatment, as suggested in the Global Initiative for Asthma (GINA) guidelines (29), have also been used for epidemiologic purposes (30). OA severity was classified by Moscato et al. on the basis of symptom frequency, activity limitation, PEF rates, FEV_1 values, and PEF variability (7). In this study, we chose to use a two-level classification of OA severity, based on FEV_1 and PD_{20} methacholine values, inspired from proposals for impairment evaluation in the USA, Quebec province of Canada, and France (31-33). This choice was motivated by the high prognostic value of the level of nonspecific bronchial hyperresponsiveness (5,34). Two recent studies have shown that PD_{20} or PC_{20} (provocative concentration causing a 20% fall in FEV_1) methacholine at diagnosis seems to be the best predictor of airway responsiveness at follow-up (35,36). The symptom score was not used in the two-level classification of OA severity in order to facilitate objective measurements. However, it was closely correlated with severity on multivariate analysis. Inhaled corticosteroid therapy at diagnosis was also correlated with severity, as treated patients had more severe disease.

In our study, age was not correlated with severity, confirming previous results from Moscato et al. (7). The role of the molecular weight of the causal allergen in the severity of OA at diagnosis or on outcome has been poorly investigated (37). In a prospective study, Perfetti et al. found a less favorable outcome when the causal agent was a high molecular weight allergen (38). However, a recent survey from the same team did not confirm these findings (36). In our study, the distribution of causal allergens according to their molecular weight did not differ between the two groups, and molecular weight did not appear to be a factor associated with severity on multivariate analysis.

Atopy, which is known to increase the likelihood of sensitization to high molecular weight agents, was not correlated with asthma severity, in accordance with previous studies (7,30).

Duration of symptoms before diagnosis is closely correlated with duration of exposure after the first asthma symptoms. Unlike Moscato et al. (7), we found a significant positive association between the duration of symptoms before diagnosis and severity of OA at diagnosis. It has also been demonstrated that a long duration of symptoms before diagnosis could be a determinant of an unfavorable outcome from different causes of OA, after avoidance of exposure (36,38-40).

In conclusion, severity of OA with latency period at diagnosis was not associated with age, smoking habits, atopy, or molecular weight of causal allergen. The only relevant factor associated with severity was the duration of symptoms before diagnosis. This finding, in conjunction with the fact that a long duration of symptoms before diagnosis is also an important adverse prognostic factor, emphasizes the need for early diagnosis and avoidance of exposure.

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		Total	Mild group	Moderate-severe group	
		n=229	n=128 (55.9%)	n=101 (44.1%)	P=*
Gender, n= (%)	*Male*	134 (58.5)	71 (55.5)	63 (62.4)	NS
	Female	95 (41.5)	57 (44.5)	38 (37.6)	
Age (years)	*Mean (sd)*	39.0 (11.4)	38.6 (11.4)	39.4 (11.4)	NS
Smoking habits, n= (%)	*Non-smoker*	115 (53.0)	68 (55.7)	47 (49.5)	*0.06*
	Current smoker	48 (22.1)	20 (16.4)	28 (29.5)	
	Ex-smoker	54 (24.9)	34 (27.9)	20 (21.0)	
	(missing data)	*12*			
	PA: m (sd)	13.6 (12.4)	14.7 (12.8)	12.5 (11.9)	NS
Atopy, n= (%)	*No*	114 (49.8)	70 (54.7)	44 (43.6)	0.09
	Yes	115 (50.2)	58 (45.3)	57 (56.4)	
Molecular weight of the suspected allergen, n= (%)	*Low*	130 (58.3)	75 (61.0)	55 (55.0)	NS
	High	93 (41.7)	48 (39.0)	45 (45.0)	
Company size, n= (%)	*<50 workers*	143 (62.5)	73 (57.0)	70 (69.3)	0.06
	≥ 50 workers	86 (37.5)	55 (43.0)	31 (30.7)	
Duration of exposure before symptoms (years)	*Mean (sd)*	8.5 (8.7)	8.4 (8.7)	**8.6 (8.8)**	NS
Duration of symptoms before diagnosis (years)	*Mean (sd)*	4.7 (5.7)	3.4 (4.4)	**6.3 (6.8)**	**0.0001**
Treatment by inhaled corticosteroids at diagnosis, n= (%)	*No*	128 (55.9)	**83 (64.8)**	**45 (44.6)**	**0.02**
	Yes	101 (44.1)	**45 (35.2)**	**56 (55.4)**	
Symptom score	*Mean (sd)*	21.2 (7.1)	**22.4 (7.5)**	**19.5 (6.1)**	**0.01**
FEV_1 (as % predicted)	*Mean (sd)*	88.9 (19.2)	**95.2 (13.5)**	**81.0 (22.3)**	**<0.0001**
FEF25-75 (as % predicted)	*Mean (sd)*	71.7 (28.0)	**80.6 (24.4)**	**60.2 (28.4)**	**<0.0001**
FEV_1 /FVC x100	*Mean (sd)*	77.6 (11.4)	**80.9 (7.7)**	**73.3 (13.7)**	**<0.0001**
PD20 methacholine (µg)	*Mean (sd)*	649 (578)	**953 (544)**	**158 (69)**	**<0.0001**

Table 1. Characteristics of the sample and bivariate comparisons between mild and moderate-severe groups of immunologic occupational asthma.

* Chi-square and Student t tests, NS= not significant,

FEV_1= Forced Expiratory Volume in one second, FEF25-75=Forced Expiratory Flow between 25 and 75 of Forced Vital Capacity (FVC), PD_{20} methacholine =provocative dose of methacholine causing a 20% fall in FEV_1.

		Total n=229 (100%)		Mild group n=128 (55.9%)		Moderate-severe group n=101 (44.1%)	
		n =	%	n =	%	n =	%
Causes	*flour*	55	*24,0*	29	*22.7*	26	*25.7*
	persulfate salts	33	*14.4*	18	*14.1*	15	*14.9*
	isocyanates	28	*12.2*	14	*10.9*	14	*13.9*
	latex	16	*7,0*	9	*7,0*	7	*6.9*
	amines	15	*6.6*	10	*7.8*	5	*5,0*
	quaternary ammoniums	14	*6.1*	11	*8.6*	3	*3,0*
	aldehydes	13	*5.7*	10	*7.8*	3	*3,0*
	mites	11	*4.8*	4	*3.1*	7	*6.9*
	resins & glues (isocyanates excluded)	8	*3.5*	3	*2.3*	5	*5,0*
	laboratory animals	5	*2.2*	3	*2.3*	2	*2,0*
	pollens	5	*2.2*	3	*2.3*	2	*2,0*
	others	26	*11.3*	14	*11.1*	12	*11.7*
Jobs	*bakers and pastry makers*	53	*23.1*	28	*21.9*	25	*24.8*
	hairdressers	37	*16.2*	21	*16.4*	16	*15.8*
	health workers	24	*10.5*	14	*10.9*	10	*9.9*
	cleaners	22	*9.6*	13	*10.2*	9	*8.9*
	painters (mainly spray painters)	13	*5.7*	6	*4.7*	7	*6.9*
	laboratory technicians	6	*2.6*	4	*3.1*	2	*2,0*
	wood workers	7	*3.1*	3	*2.3*	4	*4,0*
	welders	5	*2.2*	2	*1.6*	3	*3,0*
	others	62	*27,0*	37	*28.9*	25	*24.7*

Table 2. Distribution of causes and jobs in the study population.

		Total n=229	Probable OA n=167 (72.9%)	Definite OA n=62 (27.1%)	p=*
Gender, n= (%)	*Male*	134 (58.5)	96 (57.5)	38 (61.3)	NS
	Female	95 (41.5)	71 (42.5)	24 (38.7)	
Age (years)	*Mean (sd)*	39.0 (11.4)	38.9 (11.4)	39.1 (11.5)	NS
Smoking habits, n= (%)	*Non-smoker*	115 (53.0)	87 (56.1)	28 (45.2)	*NS*
	Current smoker	48 (22.1)	33 (21.3)	15 (24.2)	
	Ex-smoker	54 (24.9)	35 (22.6)	19 (30.7)	
	(missing data)	*12*			
	PA: m (sd)	13.6 (12.4)	12.8 (12.8)	15.3 (11.5)	NS
Atopy, n= (%)	*No*	114 (49.8)	80 (47.9)	34 (54.8)	NS
	Yes	115 (50.2)	87 (52.1)	28 (45.2)	NS
Molecular weight of the suspected allergen, n= (%)	*Low*	130 (58.3)	91 (55.8)	39 (65.0)	NS
	High	93 (41.7)	72 (44.2)	21 (35.0)	
Company size, n= (%)	*<50 workers*	143 (62.5)	107 (64.1)	36 (58.1)	NS
	≥ 50 workers	86 (37.5)	60 (35.9)	26 (41.9)	
Duration of exposure before symptoms (years)	*Mean (sd)*	8.5 (8.7)	8.2 (8.2)	9.2 (10.0)	NS
Duration of symptoms before diagnosis (years)	*Mean (sd)*	4.7 (5.7)	4.8 (5.9)	4.4 (5.2)	NS
Treatment by inhaled corticosteroids at diagnosis, n= (%)	*No*	128 (55.9)	95 (56.9)	33 (53.2)	NS
	Yes	101 (44.1)	72 (43.1)	29 (46.8)	
Symptom score	*Mean (sd)*	21.2 (7.1)	21.3 (7.7)	20.9 (5.7)	NS
FEV_1 (as % predicted)	*Mean (sd)*	88.9 (19.2)	89.0 (19.7)	88.7 (18.0)	NS
FEF25-75 (as % predicted)	*Mean (sd)*	71.7 (28.0)	73.1 (28.9)	67.8 (25.5)	NS
FEV_1 /FVC x100	*Mean (sd)*	77.6 (11.4)	77.6 (12.1)	77.6 (9.0)	NS
PD20 methacholine (µg)	*Mean (sd)*	649 (578)	647 (576)	654 (589)	NS
Severity group	*Mild group*	167 (72.9)	93 (55.7)	35 (56.5)	NS
	Moderate-severe group	62 (27.1)	74 (44.3)	27 (43.5)	
Positive immunologic testing	*No*	55 (37.7)	41 (36.9)	14 (40.0)	NS
	IgE or skin-prick test	91 (62.3)	70 (63.1)	21 (60.0)	
	(missing data)	83			

Table 3. Comparisons of the characteristics of subjects with probable and definite occupational asthma (OA)

* Chi-square and Student t tests, NS= not significant

FEV_1= Forced Expiratory Volume in one second, FEF25-75=Forced Expiratory Flow between 25 and 75 of Forced Vital Capacity (FVC), PD_{20} methacholine =provocative dose of methacholine causing a 20% fall in FEV_1.

		aOR [95% CI] *(for moderate-severe OA)*	p
Gender	*Male*	1	NS
	Female	0.85 [0.46-1.57]	
Age (years)	*Mean (sd)*	0.99 [0.96-1.02]	NS
Smoker (present and ex)	*No*	1	NS
	Yes	1.09 [0.60-2.00]	
Atopy	*No*	1	NS
	Yes	1.39 [0.73-2.66]	
Molecular weight of causal allergen	*Low*	1	NS
	High	0.82 [0.42-1.60]	
Duration of exposure before symptoms (years)	*Mean (sd)*	1.01 [0.97-1.05]	NS
Duration of symptoms before diagnosis (years)	*Mean (sd)*	**1.12 [1.05-1.19]**	**0.0004**
Treatment by inhaled corticosteroids at diagnosis	*No*	1	**0.04**
	Yes	**1.83 [1.01-3.33]**	
Symptom score	*Mean (sd)*	**0.93 [0.89-0.98]**	**0.01**

Table 4. Multivariate analyses using a logistic model based on severity of immunologic occupational asthma (OA).
NS= not significant