

Original article

Features and severity of occupational asthma upon diagnosis: an Italian multicentric case review

Background. The severity of occupational asthma (OA) at the time of diagnosis is not known. In this study we aimed to evaluate some features of the disease at the time of diagnosis, particularly looking at severity and treatment before diagnosis.

Methods: Medical records of subjects ($n=197$) who had received a diagnosis of OA in six specialized centres of Northern and Central Italy in the period 1992–97 were reviewed. The severity of the disease at the time of diagnosis was determined on the basis of symptoms, peak expiratory flow (PEF, percentage predicted), forced expiratory volume in one second (FEV₁, percentage predicted), and PEF variability, following the criteria of the National Institutes of Health and World Health Organization (NIH/WHO) guidelines on asthma. Medications used in the month before diagnosis were recorded.

Results: The most common etiological agents were isocyanates (41.6%), flours (19.8%), woods (9.7%) and natural rubber latex (7.6%). The level of asthma severity (AS) was mild intermittent in 23.9% patients, mild persistent in 28.9%, moderate in 41.6%, and severe in 5.6%. Asthma severity was positively associated with current or previous smoking ($P<0.05$), and was not related to atopy and current exposure. A relationship with bronchial reactivity to methacholine was shown in subjects at work. Treatment before diagnosis was consistent with the NIH/WHO guidelines in only 13.2% patients, whereas 75.6% were undertreated and 11.2% were overtreated.

Conclusions: In this study we found that the majority of patients had mild asthma at the time of diagnosis and that cigarette smoking was associated with a greater severity. Moreover, the majority of patients were undertreated before etiological diagnosis.

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Occupational asthma (OA) has become the most prevalent occupational lung disease in developed countries, accounting for 26% (1) to 52% (2) of all occupational respiratory diseases.

Several studies have described the characteristics of OA at the time of diagnosis, nevertheless the severity of the disease at diagnosis has not yet been investigated, despite the fact that it is a remarkable factor for the prognosis (3). In addition, knowledge of factors affecting severity might have important implications for the management of the disease. This is particularly

relevant in OA, which has not only medical but also socioeconomic and psychological consequences (4, 5). Furthermore, OA represents a good model to study the natural history of asthma because the onset of the disease is well defined, the etiological agents can be identified and the occupational exposure can be monitored, controlled and eventually abolished.

In this retrospective study we aimed to describe the features of OA in a group of subjects diagnosed in six centres of Northern and Central Italy (which have expertise in occupational asthma), and, in particular, to

evaluate the degree of asthma severity at the time of diagnosis, as well as the factors that may have influenced severity and the level of treatment before diagnosis.

Material and methods

Subjects

Data concerning occupational and clinical history, atopy, functional tests and specific diagnostic procedures of 251 patients with OA diagnosed in six specialized centres of Northern and Central Italy in the years 1992–97 were obtained from the original medical records.

The following factors were registered: sex, age, smoking habits, type of employment, field of activity, occupational hazards, duration of employment and exposure, duration of symptoms, interval between last exposure and examination, stop–resume work test, and medications taken during the month preceding first examination. The results of allergy skin prick tests (6) for common aeroallergens (7) and for specific occupational allergens, when available, were also registered.

The values of forced expiratory volume in one second (FEV₁) and peak expiratory flow (PEF) measured at the time of diagnosis and expressed as percentages of predicted values (7, 8) were collected. Bronchial responsiveness to methacholine (Mch), expressed as the provocative dose (PD) causing a 20% fall in FEV₁ (PD₂₀ FEV₁, µg of Mch), was recorded. Methacholine challenge was performed with a dosimeter method, according to the standardization guidelines of the European Respiratory Society (9), when baseline FEV₁ was ≥ 70% of predicted. It was noted whether the test was performed during a working period (at work) or after work had been stopped for more than two weeks (out of work).

The nomenclature employed in this paper to describe the characteristics of the subjects conforms to the revised nomenclature for allergy proposed by the EAACI (10).

Diagnosis of occupational asthma

To ensure homogeneity of diagnostic criteria, only subjects satisfying the following criteria (11, 12) were included in the study: diagnosis of asthma, onset of asthma after entering the workplace, association

between symptoms of asthma and work, workplace exposure to an agent known to give rise to OA, positive response to specific bronchial provocation test (BPT) or to occupational-type challenge (13). Only 197 subjects out of the original 251 were eligible for the study. The other 54 cases had to be considered only as likely OA, or work-aggravated asthma (11).

The level of asthma severity (AS) was classified on the basis of diurnal and nocturnal symptom frequency, activity limitation, PEF (percentage predicted), FEV₁ (percentage predicted) and PEF variability, according to the NIH/WHO guidelines (14): level 1 = mild intermittent, level 2 = mild persistent, level 3 = moderate persistent, level 4 = severe persistent.

Statistical analysis

A chi-squared test ($m \times n$ contingency tables) was used for comparison of frequencies of qualitative variables. Nonparametric analysis of variance (Kruskal–Wallis test) and Mann–Whitney *U*-test were used to compare the values of quantitative variables. Probability values of $P < 0.05$ were considered significant.

Results

The characteristics of the patients included in the study are shown in Table 1. The same table shows the characteristics of the noneligible subjects. They were similar to the study population, except for a slightly lower FEV₁, being, however, the median values of both groups in the normal range. The majority of patients were industry workers (47.7%) and craftsmen (40.1%). Furniture and wood manufacturing comprised the greatest number of cases (39.1%), followed by food production (19.8%), the health care system (9.6%), metal carpentry (9.6%), the plastics' industry (6.6%), and hairdressing (6.6%). FEV₁ was impaired (<80% of predicted) in 20 patients (10.2%). Bronchial reactivity to methacholine was higher ($P < 0.01$) in the subjects tested at work than in those tested out of work.

Table 1. Characteristics of the patients

	Study population	Non-eligible subjects
Patients <i>n</i>	197.0	54.0
Males <i>n</i> (%)	132.0 (67.0)	34.0 (63.0)
Females <i>n</i> (%)	65.0 (33.0)	20.0 (37.0)
Age§	35.0 (27.0–46.0)	38.0 (27.7–48.5)
Atopic subjects <i>n</i> (%)	63.0 (32.0)	30.0 (55.6)
Smokers <i>n</i> (%)	39.0 (19.8)	13.0 (24.1)
Ex-smokers <i>n</i> (%)	66.0 (33.5)	11.0 (20.3)
Non-smokers <i>n</i> (%)	92.0 (46.7)	30.0 (55.6)
Currently exposed <i>n</i> (%)	168.0 (85.3)	43.0 (79.6)
Duration of exposure (years)§	11.0 (4.0–21.0)	12.5 (5.7–20.7)
Duration of symptoms (months)§	24.0 (12.0–63.0)	24.0 (12.0–84.0)
FEV ₁ (observed/predicted × 100)§	100.0 (90.0–109.5)**	91.0 (72.0–99.2)**
PD ₂₀ FEV ₁ (µg of Mch)§	371.0 (112.5–1671.8) (<i>n</i> = 177)	391.0 (160.0–895.0) (<i>n</i> = 37)
PD ₂₀ FEV ₁ at work (µg of Mch)§	266.6 (82.7–1061.0)* >(<i>n</i> = 100)	300.0 (60.0–855.0) (<i>n</i> = 15)
PD ₂₀ FEV ₁ out of work (µg of Mch)§	556.0 (162.0–3400.0)* (<i>n</i> = 81)	454.0 (160.0–2935.0) (<i>n</i> = 15)
Mild asthma (AS1–2) <i>n</i> (%)	104.0 (52.8)	28.0 (51.9)
Moderate–severe asthma (AS3–4) <i>n</i> (%)	93.0 (47.2)	26.0 (48.1)

§ Median (25th–75th percentiles).

* $P < 0.01$, Mann–Whitney *U*-test.

** $P < 0.01$, Mann–Whitney *U*-test.

Table 2. Characteristics of the patients according to asthma severity

	Asthma severity (AS)			
	1 Mild intermittent (<i>n</i> = 47)	2 Mild persistent (<i>n</i> = 57)	3 Moderate (<i>n</i> = 82)	4 Severe (<i>n</i> = 11)
Males <i>n</i> (%)	30.0 (22.7)	43.0 (32.6)	52.0 (39.4)	7.0 (5.3)
Females <i>n</i> (%)	17.0 (26.1)	14.0 (21.5)	30.0 (46.2)	4.0 (6.2)
Age §	34.0 (26.0–46.0)	34.0 (26.0–46.7)	35.0 (27.7–45.2)	31.0 (27.0–41.0)
Smoking habit				
Smokers <i>n</i> (%)	6.0 (12.8)	9.0 (15.8)	21.0 (25.6)	3.0 (27.3)
Ex-smokers <i>n</i> (%)	15.0 (31.9)	18.0 (31.6)	28.0 (34.2)	5.0 (45.4)
Non-smokers <i>n</i> (%)	26.0 (55.3)	30.0 (52.6)	33.0 (40.2)	3.0 (27.3)
Atopic subjects <i>n</i> (%)	13.0 (27.7)	20.0 (35.0)	27.0 (32.9)	3.0 (27.3)

§ Median (25th–75th percentiles).

The confirmation of OA was obtained by specific BPT in 109 cases (55.3%), by occupational-type challenge in 88 (44.7%). The response to specific BPT or occupational-type challenge was immediate in 72 (36.5%) cases, late in 66 (33.5%), dual in 34 (17.3%), immediate-sustained in 19 (9.6%), and progressive in 6 (3.1%).

The most common etiological agents were isocyanates (41.6%), followed by flours (19.8%) and woods (9.7%). Other agents were natural rubber latex (7.6%), persulfates (4.6%), disinfectants and detergents (4.1%), drugs (2.0%), cyanoacrylates (1.5%), vegetable derivatives (1.0%), metals (1.0%), animal derivatives (0.5%), amines (0.5%), anhydrides (0.5%), and mixed materials (5.6%). The proportion of cases due to agents acting

through IgE-mediated mechanisms (i.e. flours, latex, vegetable and animal derivatives, and anhydrides) significantly increased ($P < 0.01$) from 19.8% in 1992–93 to 60.0% in 1996–98. The largest increases concerned natural rubber latex (from 3.5% to 24.0%), cereal flours (from 15.1% to 36.0%) and persulfates (from 4.7% to 12.0%). By contrast, asthma due to agents not acting through an IgE-mediated mechanism decreased over the years of the study, the largest decrease concerning isocyanate-induced asthma (55.8% in 1992–93, 20.0% in 1996–98, $P < 0.001$).

The distribution of patients according to the four asthma severity levels is reported in Tables 2 and 3. Significant differences among the four groups were found in FEV₁ and in bronchial reactivity to methacho-

Table 3. Clinical history and functional data of the patients according to asthma severity

	Asthma severity			
	1 Mild intermittent (<i>n</i> = 47)	2 Mild persistent (<i>n</i> = 57)	3 Moderate (<i>n</i> = 82)	4 Severe (<i>n</i> = 11)
Duration of exposure (yrs)†	6.5 (4–19.2)	13.0 (4.5–23.5)	12.0 (4–21.2)	10.0 (5–18)
Duration of exposure before symptoms (yrs)†	6.0 (3–16.7)	5.5 (2.5–7.7–15)	10.0 (3–19.2)	8.0 (2–18)
Duration of symptoms before diagnosis (yrs)†	2.0 (1–5)	2.5 (1–5)	2.2 (1–6)	2.0 (1–8)
Currently exposed <i>n</i> (%)	38.0 (80.9)	49.0 (86)	72.0 (87.7)	9.0 (81.8)
FEV ₁ (observed/predicted × 100)‡	100.0 (95.0–110)‡	102.0 (94.5–111)‡	98.0 (84.7–110)‡	82.0 (57–90)‡
PEF (observed/predicted × 100)‡	91.9 (83.7–100.7)	93.5 (82.7–104)	92.0 (79.0–107)	73.0 (57–93)
*SD-PD ₂₀ FEV ₁ at work (µg of Mch)† (<i>n</i> = 100)	419.5 (236.2–1176.7) (<i>n</i> = 20)**#	174.0 (45.4–813) (<i>n</i> = 21)#	310.0 (83.4–1353) (<i>n</i> = 53)#	65.8 (37.7–05.4)# (<i>n</i> = 6)***
*SD-PD ₂₀ FEV ₁ out of work (µg of Mch)† (<i>n</i> = 83)	840.0 (360–3400) (<i>n</i> = 23)**	383.0 (166–2684.5) (<i>n</i> = 33)***	720.0 (100–3400) (<i>n</i> = 23)	87.5 (<i>n</i> = 2)
Pattern of response to specific BPT <i>n</i>				
Immediate <i>n</i> (%)	13.0 (27.7)	25.0 (43.9)	27.0 (32.9)	7.0 (63.6)
Late <i>n</i> (%)	23.0 (48.9)	19.0 (33.3)	23.0 (28.1)	1.0 (9.1)
Dual <i>n</i> (%)	10.0 (21.3)	7.0 (12.3)	16.0 (19.5)	1.0 (9.1)
Immediate-sustained <i>n</i> (%)	1.0 (2.1)	4.0 (7)	12.0 (14.6)	2.0 (18.2)
Progressive <i>n</i> (%)	0.0 (0.0)	2.0 (3.5)	4.0 (4.9)	0.0 (0.0)

† Median(25th – 75th percentiles).

‡ $P < 0.001$, Kruskal–Wallis nonparametric analysis of variance.# $P < 0.02$, Kruskal–Wallis nonparametric analysis of variance.** $P < 0.05$, Mann–Whitney U-test.*** $P < 0.05$, Mann–Whitney U-test.

Table 4. Distribution of AS according to etiological agents. $P=0.057$, chi-squared test

Agent	Mild asthma (AS 1-2) <i>n</i> (%)	Moderate to severe asthma (AS 3-4) <i>n</i> (%)
Isocyanates (<i>n</i> = 82)	44 (53.7)	38 (46.3)
Flours (<i>n</i> = 39)	22 (56.4)	17 (43.6)
Woods (<i>n</i> = 19)	14 (73.7)	5 (26.6)
Latex and other vegetable derivatives (<i>n</i> = 17)	11 (64.7)	6 (35.3)
Disinfectants, detergents and drugs (<i>n</i> = 12)	3 (25.0)	9 (75.0)
Other agents (<i>n</i> = 17)	5 (29.4)	12 (70.6)
Mixed materials (<i>n</i> = 11)	5 (45.5)	6 (54.5)
Total	104 (52.8)	93 (47.2)

line in the subjects tested at work. Atopy and durations of exposure, symptoms and latency period were not related to the degree of asthma severity. The proportion of subjects removed from exposure did not vary significantly depending on asthma severity.

The distribution of AS according to etiological agents was assessed by grouping together AS level 1 and 2 (mild asthma) and level 3 and 4 (moderate to severe asthma). (Table 4). Moderate to severe asthma appeared to be more frequent in asthma due to disinfectants, detergents and drugs (considered together), mixed materials, other agents (persulfates, cyanoacrylates, metals, animal derivatives, amines and anhydrides, considered together because of the small number of cases); however, the difference failed to reach statistical significance. Distribution of AS levels did not vary significantly also according to the mechanism of action of the responsible agent: moderate and severe asthma were 43.1% in cases caused by agents with proven IgE-mediated action (flours, latex, vegetable and animal derivatives, and anhydrides), 41.7% in cases from agents with possible IgE-mediated action (woods, metals, drugs and mixed materials), and 51.5% in cases from agents with no demonstration of IgE-mediated action (isocyanates, disinfectants, detergents, amines, cyanoacrylates, and persulfates). Grouping the subjects in the same way, no difference was found in the distribution of patterns of response to specific BPT or occupational-type challenge, being the responses other than immediate 63.5% in mild asthma and 63.4% in moderate to severe asthma.

Considering the fields of activity, AS levels 3 and 4 were the most frequent in industries involving pharmaceuticals (83.3%), metal carpentry (68.4%) and plastics (69.2%), and in hairdressers (61.5%) and farmers

(100%). However, only those from the wood and furniture industry had an AS distribution significantly different ($P<0.05$) from the other production fields, with a marked prevalence of levels 1 and 2 (63.6% vs 45.8% in the other fields).

Smoking habit, categorized as usual into current smokers, ex-smokers and nonsmokers, did not show a significant relationship to AS distribution (Table 2). However, the proportion of current or previous smokers, considered together, was significantly higher ($P<0.05$, chi-squared test) in the group of subjects with moderate to severe disease (61.3%), compared to the subjects with mild disease (46.2%). The proportion of subjects with normal pulmonary function ($FEV_1\% > 80$) was similar in nonsmokers (92.4%) and in current or previous smokers (87.6%).

A large proportion of patients (76; 38.6%) reported no treatment in the month before the first examination, 57(28.9%) had been treated with β_2 -agonists p.r.n. alone, 13 (6.6%) with β_2 -agonists regularly, 11 (5.6%) with cromolyn sodium or nedocromil sodium regularly plus β_2 -agonists as needed, 28 (14.2%) had taken inhaled corticosteroids regularly plus β_2 -agonists, 11 (5.6%) systemic corticosteroids, and 1 (0.5%) antihistamines. Considering AS levels, the therapy before diagnosis was consistent with the NIH/WHO guidelines in only 26 patients (13.2%), whereas 149 (75.6%) were undertreated and 22 (11.2%) were overtreated. Undertreatment was significantly ($P<0.001$) more frequent in moderate to severe asthma (88.2%) than in mild asthma (64.4%). Table 5 shows the medications taken during the month preceding the first examination.

Discussion

In this study we retrospectively reviewed the characteristics of OA at the time of diagnosis, paying particular attention to the severity of the disease.

The patients were from a group of referral centres for the diagnosis and management of OA, located in a wide area including North and Center of Italy. The Italian system for OA compensation requires confirmation of diagnosis by these centres to take into account the claim, thus nearly all subjects considered by their physicians to be at high suspicion of having OA are referred to these

Table 5. Treatment in the month before first examination

Treatment	Number	%
No treatment	76	38.6
β_2 -agonists as needed	57	28.9
β_2 -agonists regularly	13	6.6
Cromolyn or nedocromil sodium regularly plus β_2 -agonists as needed	11	5.6
Inhaled corticosteroids regularly plus β_2 -agonists	28	14.2
Systemic corticosteroids	11	5.6
Antihistamines	1	0.5

centres. We can assume, therefore, that these patients reflect the population of subjects with OA for each area. Out of a total of 251 records only 197 patients were included in the study. Fifty-four were excluded because they lacked clear demonstration of a cause and effect relationship between exposure and asthma (11, 12).

The areas in which the centres are located include both rural and highly industrialized environments, and the occupations of patients reflect this fact. The distribution of frequencies of etiological agents is similar to that of other European countries for the years considered in the study, whereby isocyanates and flours were reported to be the predominant causes of OA (15, 16).

Changes in the proportions of asthma with time due to various agents were observed. In particular cases due to isocyanates showed a downward trend, probably because of increasing knowledge of their sensitizing effects, leading on the one hand to substitution with other materials, and on the other hand to improved medical surveillance and preventive measures (17, 18) for exposed workers. By contrast, the number of cases due to latex increased over the years, according to the general trend in latex allergy observed in medical and nonmedical environments (19). This can be explained partly by an increase in the number of workers who are exposed, because of the more widespread use of latex devices as protection against viral infections. Nevertheless, we cannot exclude the possibility that changes in the properties of latex may also play a role (19). We also found an increase in the proportion of cereal flour asthma, which might reflect a real trend in bakeries and the baking industries, as suggested by other reports by European authors (20).

In this study we were particularly interested in evaluating the degree of asthma severity at the time of diagnosis. We are unaware of previous studies on the severity of OA.

Categorization of the severity of asthma is difficult and is still under discussion (21). In this study we used the criteria of the most recent International Guidelines for adult patients with asthma, which also include criteria for appropriate treatment (14). We found that most patients (52.8%) had mild asthma, which was intermittent (level 1) in 23.9%, and persistent (level 2) in 28.9%; 41.6 had moderate asthma; and only 5.6% of subjects had severe asthma. Due to the long duration of exposure (median 11.0 years) and symptoms (median 24.0 months) one could expect a more severe degree of disease in these patients. We might suppose a healthy-work effect (22), i.e. that the most severe patients had left work spontaneously without referring to their GP for work-related asthma. It could be argued that we investigated a selected population of subjects, i.e. those patients able to undergo specific BPT or occupational-type exposure challenge, thus excluding the patients with more severe asthma. This does not

seem to be the case, since the distribution of asthma severity was similar in the 197 subjects who took part in the study and in the 54 excluded subjects.

Considering other asthma features we found that the severity of asthma had a relationship with bronchial hyperreactivity only in subjects tested at work, i.e. the higher the hyperreactivity to methacholine the higher the degree of severity. The degree of bronchial reactivity to methacholine was significantly higher in subjects tested at work in comparison with out of work subjects, but only in the groups with a lower degree of severity (AS 1 and 2). From these findings it would seem that nonspecific bronchial hyperreactivity is an effect of exposure, which improves when subjects avoid exposure, but only in asthmatics with a low degree of severity (mild intermittent or mild persistent). Although a correlation between the severity of asthma and bronchial hyperresponsiveness is a common feature in asthma, the overall correlation may not necessarily apply to individual patients (23, 24). This is particularly true in the instance of OA, in which several cases without bronchial hyperresponsiveness have been described (25, 26).

Other characteristics of the patients were not related to severity. The average duration of symptoms before diagnosis was not significantly different among the four groups. The severity of symptoms did not seem to have influenced the cessation of exposure, since the proportion of subjects who had already been removed from exposure at the time of diagnosis did not show a significant relationship to asthma severity. Furthermore, no significant relationship was found between severity and the type of etiological agent, indicating that probably the overall conditions of exposure play a major role in determining AS.

A different distribution of AS was observed in the various occupations. This might be related to the presence of different preventive programmes in the workplace, possibly depending on the relevance of respiratory risks. Indeed, the furniture and wood industries, which have some of the most well known respiratory hazards such as isocyanates and woods, showed a higher prevalence of mild asthma, possibly because of more strict environmental control. Different levels of awareness of respiratory hazards, involving different behaviours and environmental conditions in the workplace, may lead to different patterns of exposure to the offending agents.

Cigarette smoking has been shown to be a risk factor for OA due to some agents inducing an IgE response, by interacting with atopy to increase risk among exposed individuals (27, 28), whereas it has been reported to be inversely associated with OA caused by low molecular weight compounds not inducing an IgE response (29–31). In our subjects we showed that current or previous smoking was associated with more severe OA. A possible explanation could be an indirect influence on

parameters of severity, such as lung function and symptoms (especially cough), although smoking habit alone did not seem to be significantly associated with FEV₁ reduction in our sample of patients. The relationship between smoking and OA remains to be explained in full (32).

Looking at the treatment of asthma in our patients we found that, applying the criteria of the NHI/WHO guidelines (14), a high proportion of patients (77%) was undertreated. The treatment of OA before diagnosis has been assessed previously in a small group of subjects (33), all of them undertreated according to the same NIH/WHO guidelines (14). The results of the present study confirm those data. The high proportion of undertreated patients may be partially explained by a lack of recognition of asthma before the evaluation for OA in the specialized centres, or by difficulties in the management of the disease by the medical surveillance systems in the workplace. Although no specific guideline on OA treatment has been produced, it is assumed that the pharmacological treatment of OA is identical to other forms of asthma. Thus, patients who are not adequately treated and continue to be exposed to the etiological agents of asthma may be at particularly high risk for acute exacerbation.

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