Work-exacerbated asthma and occupational asthma: Do they really differ?

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Background: Although work-exacerbated asthma (WEA) is a prevalent condition likely to have an important societal burden, there are limited data on this condition.

Objectives: The aims of this study were (1) to compare the clinical, functional, and inflammatory characteristics of workers with WEA and occupational asthma (OA) and (2) compare health care use and related costs between workers with WEA and OA, as well as between workers with work-related asthma (WRA; ie, WEA plus OA) and those with non–work-related asthma (NWRA) in a prospective study.

Methods: We performed a prospective observational study of workers with and without WRA with a 2-year follow-up. The diagnosis of OA and WEA was based on the positivity and negativity of results on specific inhalation challenges, respectively.

Results: One hundred fifty-four subjects were enrolled: 53 with WEA, 68 with OA, and 33 control asthmatic subjects (NWRA). WEA was associated with more frequent prescriptions of inhaled corticosteroids (odds ratio [OR], 4.4; 95% CI, 1.4-13.6; $P = .009$), a noneosinophilic phenotype (OR, 0.3; 95% CI, 0.1-0.9; $P = .04$), a trend toward a lower FEV_1 (OR, 0.9; 95% CI, 0.9-1.0; $P = .06$), and a higher proportion of smokers (OR, 2.5; 95% CI, 0.96-9.7; $P = .06$) than the diagnosis of OA. The health care use of WRA and related costs were 10-fold higher than those of NWRA.

Conclusion: Workers with WEA appeared to have features of greater asthma severity than workers with OA. In contrast with OA, WEA was associated with a noneosinophilic phenotype. Both OA and WEA were associated with greater health care use and 10-fold higher direct costs than NWRA. (J Allergy Clin Immunol 2013;131:704-10.)

Key words: *Cost, health care use, occupational asthma, sputum eosinophils, work-exacerbated asthma*

Asthma is considered work related when there is a relationship between the symptoms of asthma and the workplace. Work-related asthma (WRA) encompasses both asthma that is induced by either sensitization to a specific substance (ie, sensitizer-induced occupational asthma [OA]) or exposure to an inhaled irritant at work (ie, irritant-induced OA) and pre-existing or coincidental asthma that is exacerbated by a workplace-related stimulus (ie, work-exacerbated asthma [WEA]).[1] WRA is a major public health concern because of its high prevalence and societal burden. The American Thoracic Society recently issued a statement on WEA that reported that 21.5% of workers with asthma have work-related exacerbations.[2] The 2001 and 2002 data from Breton et al[3] showed that subjects who reported having WRA in the United States were 4.8 times more likely to report having an asthma exacerbation, 4.8 times more likely to visit the emergency department at least once, and 2.5 times more likely to visit their physician for an asthma exacerbation in the previous 12 months compared with subjects with non–work-related asthma (NWRA). We also showed that subjects with WRA followed in a tertiary Canadian clinic had more visits to the clinic for asthma and hospitalizations for asthma during the year preceding their diagnosis than subjects with NWRA.[4] However, our study was based on a retrospective design, whereas the study by Breton al[3] neither included any objective confirmation of the diagnosis of asthma nor compared WEA and OA cases.

Over the past years, there have been tremendous efforts to assess different aspects of OA. However, despite the large prevalence of this condition, the data regarding WEA are much more limited. To our knowledge, there is no prospective study that has compared clinical characteristics and health care use between workers with an objectively confirmed diagnosis of OA or WEA. Whether a rigorous clinical assessment can allow distinguishing OA from WEA in clinical practice remains to be determined. Consequently, the aims of this prospective cohort study were (1) to compare the clinical, functional, and inflammatory characteristics of workers with objectively confirmed diagnoses of WEA and OA and (2) to compare health care use and related costs between workers with an objectively confirmed diagnosis of WEA and OA and between workers with WRA (ie, OA plus WEA) and NWRA.

METHODS

Study design

This was a prospective cohort study of workers with and without WRA with a 2-year follow-up.

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Abbreviations used

ACQ: Asthma Control Questionnaire
MED-ECHO: Maintenance et exploitation des données pour l'étude de la clientèle hospitalière
NWRA: Non–work-related asthma
OA: Occupational asthma
OR: Odds ratio
RAMQ: Régie de l'assurance maladie du Québec
SIC: Specific inhalation challenge
WEA: Work-exacerbated asthma
WRA: Work-related asthma

Subjects

All asthmatic subjects referred for suspected WRA in 2 tertiary centers of the province of Quebec between 2003 and 2008 were consecutively screened, enrolled, and followed for 2 years. Concomitantly, asthmatic subjects assessed for the first time in the same centers but who were not referred for WRA exacerbations and did not complain of work-related exacerbation of their respiratory symptoms were invited to participate as control subjects. The inclusion of this group allowed us to interpret whether differences between WEA and OA imply similar, greater, or lower differences relative to subjects with NWRA. Furthermore, the absence of the NWRA group would make it very difficult to appreciate the extent of the excess cost of WRA in comparison with NWRA.

During the first visit, detailed medical and occupational questionnaires were administered. Questions were asked about respiratory symptoms at work, asthma medication, smoking habits, and work environment. Standardized questionnaires about asthma control[5] and asthma quality of life[6] were assessed. Skin prick tests[7] and respiratory function tests,[8] including methacholine inhalation challenge[9] and sputum induction,[10,11] were subsequently performed. Workers were classified according to their inflammatory phenotypes: eosinophilic (sputum eosinophils ≥3%), neutrophilic (sputum neutrophils ≥61%), paucigranulocytic (sputum eosinophils <3% and sputum neutrophils <61%), and mixed (sputum eosinophils ≥3% and sputum neutrophils ≥61%).[12]

Severe asthma exacerbations were defined as an emergency department visit or a hospitalization during the study period according to the provincial administrative databases. Specific inhalation challenges (SICs)[13] to occupational agents were subsequently performed when asthma was possibly related to work to differentiate OA from WEA.

The diagnosis of asthma was retained if reversible airflow limitation was demonstrated (FEV_1 <80% of predicted value and FEV_1/forced vital capacity ratio <0.7 with an improvement in FEV_1 of ≥12% [and ≥200 mL] after bronchodilator)[14,15] or, in the absence of reversible airflow limitation, if a PC_{20} value of lower than 16 mg/mL was demonstrated. The diagnosis of OA was only based on positive SIC reactions. Subjects with a worsening of their asthma symptoms when at work and a positive SIC reaction were defined as having OA, whereas subjects with a worsening of their asthma symptoms at work and a negative SIC reaction were defined as having WEA.[16]

The study was approved by Sacré-Coeur and Laval Hospital's research ethics committees (no. 205-07-30). All subjects provided written consent.

Procedures

The clinicians who investigated the subjects were experts in the field of WRA. On the basis of open questions, the Material Safety Data Sheets, and their own experience, they identified the different potential harmful occupational agents and classified them into high- and low-molecular-weight agents. The procedures are detailed in the Methods section in this article's Online Repository at www.jacionline.org.

Assessment of health care use and related costs

An authorization was obtained from the Commission d'accès à l'information du Québec for linking the medical charts to the administrative databases provided by the Régie de l'assurance maladie du Québec (RAMQ) and Maintenance et exploitation des données pour l'étude de la clientèle hospitalière (MED-ECHO) regarding the outpatient clinic visits, visits to the emergency department, and hospitalizations during the year before and after the first visit in which the subjects were first assessed in Montreal or Quebec at Sacré-Coeur or Laval Hospital, respectively. Severe asthma exacerbations were defined by a visit to the emergency department, a hospitalization, or both for asthma.

We estimated the use and cost of the major categories of medical resources, consisting of physician's services, emergency department visits, and hospitalizations. The methodology used for calculating the costs is detailed in the Methods section in this article's Online Repository.

Statistical analysis

Continuous variables were reported as means and SDs, except for PC_{20} values, which were reported as geometric means and 95% CIs, and sputum cell counts, which were reported as medians and interquartile ranges. A χ^2 test was used to compare the categorical variables between groups.

The Student *t* test was used to compare the characteristics of continuous variables (1) between subjects with OA and those with WEA and (2) between subjects with WRA and those with NWRA. Paired analyses were conducted to compare the data at baseline and follow-up. Nonparametric tests were performed for data that were not normally distributed. Logistic regression analyses were conducted to compare the clinical, functional, and inflammatory characteristics associated with the diagnosis of WEA and OA, as well as to assess the predictors of severe asthma exacerbations occurring in the year before the diagnosis of WRA or NWRA. Because asthma severity is now classified par international guidelines[15] on the basis of treatment required to achieve good asthma control, we classified the severity of asthma in our population as mild, moderate, and severe according to their medication needs and the occurrence of severe exacerbations in the year before their enrollment in the study.

We performed a hierarchical cluster analysis using the Ward method, applying squared Euclidian distance as the distance of the similarity measure to identify the number of clusters. Differences between clusters were evaluated by using ANOVA or the Student *t* test for normally distributed continuous variables. χ^2 Analysis was used for categorical measures.

Statistical analysis was performed with the IBM SPSS statistical software (version 19.0.0; IBM, Somers, NY). Significance was accepted at a P value of .05 or less.

RESULTS

Baseline evaluation

Clinical characteristics. One hundred eighty-eight subjects were invited to participate in this study, and 34 declined to participate (16 with WRA and 18 with NWRA). One hundred fifty-four subjects were enrolled: 53 with WEA, 68 with OA, and 33 control asthmatic subjects. Their characteristics at baseline are reported in Table I, whereas the characteristics of the subjects with WEA and OA who were at or away from work at baseline are reported in Table II.

Comparison between subjects with WEA and those with OA. After adjusting for age, asthma control, and asthma severity, the diagnosis of WEA was associated with more frequent prescription of inhaled corticosteroids (odds ratio [OR], 4.4; 95% CI, 1.4-13.6; $P = .009$), a noneosinophilic phenotype (OR, 0.3; 95% CI, 0.1-0.9; $P = .04$), a trend toward a lower FEV_1 (OR, 0.9; 95% CI, 0.9-1.0; $P = .06$), and a higher proportion of smokers (OR, 2.5; 95% CI, 0.9-6.4; $P = .07$) than the diagnosis of OA. However, asthma control (OR, 0.8; 95% CI, 0.5-1.4) or asthma severity (OR, 0.6; 95% CI, 0.3-1.2; $P = .1$) were not associated with the type of diagnosis (WEA vs OA).

We did not find any clinical, functional, or inflammatory differences between subjects with WEA who had already been