Irritant-Induced Occupational Asthma*

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A retrospective review was performed on the files of 154 consecutive workers assessed for occupational asthma to clarify the relative frequency of asthma induced by irritants in the workplace and to determine whether such asthma was clearly distinguishable from other forms of occupational asthma. Fifty-nine workers were considered to have occupational asthma. A subset of ten had a history consistent with asthma initiated by exposure to high concentrations of an irritant, had persistent symptoms for an average of five years when seen, demonstrated increased reactivity to methacholine, and gave no prior history of pulmonary complaints. These ten had a lower incidence of atopy (20 percent vs 58 percent) and a more frequent history of smoking (80 percent vs 38 percent) than the other subjects with occupational asthma but did not differ in average latency (5.9 years vs 5.7 years). Our findings suggest that irritant-induced asthma is not uncommon, and those affected may have different baseline characteristics from others with occupational asthma. (Chest 1989; 96:297-300

RADS = reactive airways dysfunction syndrome; methacholine PC_{20} = concentration of methacholine inducing 20 percent fall in FEV,

Reactive airways dysfunction syndrome has been described by Brooks et al1 as an asthma-like illness following a single exposure to high levels of an irritating vapor, fumes, or smoke. Similar symptoms with obstruction of the airways were previously described in several case reports after high-dose exposure to irritants,5-10 although in some reports, bronchiolitis obliterans may have caused the obstruction of the airways.11 More recently, Boulet12 has also described a persistent increase in bronchial responsiveness following acute exposure to respiratory irritants. His findings suggest that when an irritant can also cause nonirritant asthma in low doses (eg, isocyanates), the patient may become specifically sensitized to it by the high-dose exposure. The present study undertook to determine the prevalence of irritant-induced asthma in patients being assessed for possible occupational disease of the airways and to compare patients having irritant-induced asthma with those having occupational asthma due to known sensitizers.

MATERIALS AND METHODS

A retrospective review was performed on the files of 154 consecutive workers referred for assessment of possible occupational asthma. They were all seen in the clinics of the Gage Research Institute (35 workers) and the Toronto General Hospital (119 workers) between 1978 and 1987 by one of us (S.M.T.) using the same diagnostic approach throughout.

A full history in all subjects included occupational exposure, information on any known spills or unusually high exposures, respiratory symptoms, date of onset, and temporal relationship to the workplace. Smoking history, upper respiratory symptoms, history of respiratory symptoms, and family history of allergy were also included, and a full physical examination was performed.

Skin testing was done by the prick method using a group of 16 common allergenic extracts (Bencard) and diluent in all patients. Additional skin tests were performed with known allergens or potential allergens present in the individual's workplace. A positive skin test was taken as a weal 2 mm or more larger in diameter than that of the control response, with a surrounding flare.

Baseline pulmonary function tests were performed in all patients at the initial visit, consisting of spirometry, pulmonary volumes, and diffusing capacity. Challenge testing with methacholine inhalation was done using the method described by Juniper and colleagues.13 A methacholine PC_{20} of 8 mg/ml or less was taken to indicate bronchial hyperresponsiveness.

Where possible, methacholine challenges were repeated within 48 hours after a day at work and after 10 to 14 days off work. A shift in methacholine PC_{20} more than fourfold was considered significant in the absence of any confounding factors such as respiratory tract infections. If the baseline FEV, was 50 percent of predicted or less or 1 L or less or if the FEV/N ratio was 50 percent or less, the methacholine challenge was not done, but spirometry was repeated 15 minutes after administration of a beta-adrenergic inhaler (albuterol [salbutamol]; 400 microg). An increase of 15 percent or more in FEV from baseline was taken to indicate reversible airflow limitation. A bronchodilator response to albuterol was also performed in those patients unable or unwilling to discontinue their bronchodilator medications long enough for a methacholine challenge to be performed (ranging from eight hours prior to challenge for inhaled beta-adrenergic agents to 48 hours for slow-release theophylline preparations).

In patients who were still at work with continuing exposure to similar amounts of the suspected causative agent as reported in the history and in those who had left but could return to the former work environment, studies of peak flow at home and at work were performed over a four-week period using a peak flowmeter (either a Wright or mini-Wright peak flowmeter [Armstrong Medical Industries], an Assess peak flowmeter, or a Spira peak flowmeter [Trudell Medical]). Patients were asked to record the highest of three readings at home and at work four times per day prior to the use of any inhalers and, additionally, if awakened from sleep by symptoms. The subjects also recorded inhaler use and any changes in medication and indicated their location at the time of the readings. A reduction in peak flow rates of 20 percent or more on working days, compared with readings at the same time of day when off of work, on at least three days per week was considered a positive record.

Occupational inhalation challenges were performed in selected

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patients using the method of Pepys and Hutchcroft in trying to reproduce the workplace exposure in the laboratory. These were performed in patients who could not return to their former workplace, in whom (1) the history was atypical for occupational asthma, (2) the history was suggestive, but no objective evidence for asthma was available, or (3) the suspected agent was not recognized to cause occupational asthma. Challenges were not performed in patients with irritant-induced asthma, as the implicated levels of chemicals were thought to be above the TLV.

Safety data sheets on the workplace chemicals and, where possible, representative sampling of workplace levels were provided by the Ontario Ministry of Labour and the Ontario Workers’ Compensation Board.

The criteria used for a diagnosis of sensitiser-induced occupational asthma were as follows: (1) absence of previous asthmatic complaints; (2) onset of symptoms within 24 hours of reexposure to a workplace sensitiser (a substance which can induce asthma in susceptible levels) following a latent period of asymptomatic exposure; (3) symptoms of cough, wheeze, or dyspnea improving consistently when away from work; (4) airflow limitation on pulmonary function tests improving with bronchodilator, or presence of bronchial hyperresponsiveness (or both); and (5) at least one of the following, when possible: (a) changes in peak flow or methacholine response related to workplace exposure; (b) positive skin test to workplace allergens; or (c) positive bronchial challenge with workplace materials. If the first three criteria were present but objective confirmation was not available, a diagnosis of possible occupational asthma was made.

Criteria for the diagnosis of irritant-induced asthma were modified from Brooks et al. The criteria differed from those used for occupational asthma in respect to criteria 2, 3, and 5, as follows: (2) onset of symptoms within 24 hours of an exposure, in the workplace, to a high concentration of an inhaled irritant on one or more occasions; (3) symptoms of cough, wheeze, and dyspnea persisting for at least three months; (5) if workplace exposure when seen was comparable to that at the onset of symptoms, then changes in peak flow or methacholine response (or both) were assessed; changes related to workplace exposure were included as one of the criteria; and (6) other pulmonary diseases excluded.

Unlike Brooks et al, exposure was not limited to a single accident or incident at work. None of our patients underwent bronchial biopsies.

Possible irritant-induced asthma was diagnosed in those with a suggestive history whose duration of symptoms was less than three months or those in whom the pulmonary function and bronchial responsiveness was normal when first assessed more than three months after the onset of symptoms. Statistical analysis of the data was performed using χ² and Student’s t-tests.

RESULTS

Ten (6 percent) of the 154 patients fulfilled our criteria for irritant-induced asthma, while 49 (32 percent) had occupational asthma related to a workplace sensitizer. An additional 15 (10 percent) had possible irritant-induced asthma, and 31 (20 percent) had possible sensitizer-induced asthma, of whom 20 had objective evidence of asthma. Among the 48 (31 percent) not diagnosed as having occupational asthma, six had unrelated asthma.

Of those with sensitizer-induced asthma, 16 had methacholine changes related to workplace exposure, 19 had peak flow studies supportive of the diagnosis, and 22 had positive specific challenge tests with the suspect agent. The most common responsible agents were isocyanates (16 patients), flour (nine patients), and red cedar (six patients).

The ten patients with irritant-induced asthma had a variety of implicated causative agents (Table 1), all of which had in common the characteristic of being irritants when inhaled in high concentrations. The two workers relating symptoms to isocyanates both described unusually high levels within 15 minutes before the onset of their symptoms. One had six previous days of low-level exposure to isocyanate, while the other had no known previous exposure to isocyanates. Neither underwent challenge testing in the laboratory to determine subsequent sensitization to isocyanates. One had no further isocyanate exposure, and the other had a single further day of workplace exposure with associated symptoms of asthma, but no objective documentation was performed at that time. All of the patients were men, with a mean age of 44 years. Twenty percent (two) were atopic on the basis of positive skin tests to common allergens. The duration of exposure to varying levels of the workplace irritants ranged from one day to 27 years, although only three had exposure for over six months. Symptoms had been present for three months to 33 years, (mean, 4.8 years) when assessed and had persisted for up to three years away from work (mean, seven months). The methacholine response ranged from a PC20 of 0.03 to 8 mg/ml.

The three subjects with irritant-induced asthma who had had exposure at work for over six months before the onset of symptoms were still working when assessed and could not relate the onset to an accident or unusual event at work. Methacholine challenges at work and off work were assessed in two of these patients and showed significant improvement off work, from a PC20 of 0.03 mg/ml at work to 1.5 mg/ml off work in subject 4, and a PC20 of 2 mg/ml at work improving to more than 16 mg/ml off work in subject 5. Both had borderline improvements in peak flow off work. The third subject, subject 2, showed significant improvement in peak flow away from work but could not return for methacholine challenge. Only one further subject, subject 7, still had similar workplace exposure as at the onset of symptoms, and he too showed significant improvement in methacholine response off work (PC20, 0.2 mg/ml to 5 mg/ml). Measurement of the levels of workplace irritants during the period when the subject was at work with symptoms was performed only for one patient, subject 2. This showed calcium oxide levels ranging from 2.47 to 7.6 mg/cu m (Ontario allowable time weighted average, 2 mg/cu m).

The ten patients with irritant-induced asthma (Table 2) showed a significantly higher proportion of men and nonatopic individuals than among those with sensitizer-induced asthma. Also, a higher proportion
of those with irritant-induced asthma were smokers or ex-smokers; however, there was no significant difference in age, duration of prior work exposure, duration of symptoms, or methacholine responsiveness.

The 15 patients with possible irritant-induced asthma had exposure to similar irritant agents as the ten patients with a definite diagnosis; however, in six patients, typical symptoms lasted less than three months and when assessed, only one out of the 15 who had methacholine tests had bronchial hyperresponsiveness. The mean duration of symptoms in this group was 0.9 years, ranging up to 3.5 years. The mean interval between the onset of symptoms and the time of assessment was 1.6 years, ranging from two months to six years.

**DISCUSSION**

Our findings confirm that irritant-induced occupational asthma is not uncommon in a population of

patients referred for assessment of possible occupational disease of the airways. The incidence of 6 percent with a definite diagnosis and a further 10 percent with a possible diagnosis in our study is higher than the 2 percent definite and 6 percent suspected RADS reported by Brooks and colleagues among patients with suspected occupational or environmental asthma; however, their criteria for a definite diagnosis of RADS were more stringent than those used by us for irritant-induced asthma in that they confined exposures to a single specific incident or accident.

If our criteria had been similarly restricted, our incidence of irritant-induced asthma would be 3 percent, indicating a very similar distribution in our population. We expanded the criterion for possible exposure time in this study in the recognition that irritant levels in the workplace can fluctuate significantly, and in many industries, accidental spills are relatively common. Therefore, several workers could not identify one unusual incident within 24 hours before the onset of symptoms. Both patients with symptoms related to isocyanates described a single clear incident of unusually high exposure precipitating symptoms which we believed justified their inclusion into a diagnosis of irritant-induced asthma. Although the incident may also have sensitized these patients to isocyanates, this was not addressed in this study.

The duration of symptoms in our patients was similar to that described by Brooks and colleagues, often persisting for years. In one patient, symptoms persisted for 38 years after onset, but workplace exposure to irritants of varying levels had continued for 35 of those years. Our findings of a predominance of male subjects with this diagnosis likely reflects the population with exposure to such irritants. The presence of atopy in two out of the ten patients is identical to the findings of Brooks et al and is consistent with
a lack of allergic predisposition in irritant-induced asthma. The positive smoking history in eight out of ten patients also is slightly greater than the six out of ten in the report by Brooks et al\(^4\) and emphasizes the importance of considering significant preexisting disease of the airways due to smoking. Only three of our patients had a smoking history of more than four pack-years, and in only one was the smoking history over 15 pack-years. Nevertheless, this clearly can be a confounding factor in the diagnosis. Additionally, smoking may be a predisposing factor to the development of irritant-induced asthma, as has been suggested in some populations with occupational asthma.\(^{15,16}\)

Our patients with sensitizer-induced occupational asthma had a greater prevalence of positive skin tests to common allergens than those in the irritant-induced group, as has been noted in some other studies.\(^ {17,18} \) A lower proportion than seen in irritant-induced asthmatic subjects were smokers or ex-smokers.

The longer mean duration of symptoms in those with irritant-induced asthma than those in the sensitizer-induced group was biased by one irritant-induced asthmatic subject whose symptoms persisted for 38 years, 35 years of which he had continued to spend in the same workplace. Nevertheless, symptoms in the irritant-induced group did persist for up to three years after cessation of exposure (mean, seven months when assessed) and emphasizes that irritant-induced effects can be sustained; however, the mean duration of symptoms was further biased by the criteria requiring persistence of symptoms for three months and demonstration of bronchial hyperresponsiveness. Thus, some patients may have had irritant-induced airway hyperresponsiveness of relatively short duration with improvement in symptoms and pulmonary function before three months. Others were not assessed until more than three months after the onset of symptoms and were then asymptomatic with normal airway responsiveness. In our population, those patients with possible irritant-induced asthma were more common than those with a definite diagnosis (15 vs 10). To make a more definitive diagnosis, patients with suspected irritant-induced disease of the airways would need objective assessment as soon as possible after the onset of symptoms to document bronchial reactivity. The boundary of three-months’ duration of symptoms is useful for definition in research studies, as it is a period of time within which most patients would receive evaluation by a specialist, but it should be recognized as arbitrary in a clinical setting or in compensation claims.

Therefore, our findings indicate that irritant-induced occupational asthma has features similar to occupational asthma caused by sensitizers in that it is manifested by symptoms and pulmonary function findings which may include changes in methacholine responsiveness with workplace exposure, a feature previously considered to indicate a causation by a specific sensitizer. We consider irritant-induced occupational asthma to be a form of occupational asthma caused by a single or multiple exposure to irritants.

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REFERENCES