Asthma Experience in an Occupational and Environmental Medicine Clinic

Low-Dose Reactive Airways Dysfunction Syndrome

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The etiology of adult-onset asthma is incompletely understood. High-intensity exposure to irritants is one accepted risk factor and such cases are termed Reactive Airways Dysfunction Syndrome. The contribution to asthma of less intense and less acute exposure to irritants remains to be clarified. We report on 10 cases of nonsensitization adult-onset asthma in settings of exposure to noticeable but distinctly "tolerable" levels of inhalation irritants. This series of 10 cases represent 31% of verified asthma cases seen in our environmental and occupational medicine referral clinic over a 5-year period. We believe further exploration of this phenomenon of low dose Reactive Airways Dysfunction Syndrome is warranted.

Occupational asthma has long been recognized as an important cause of worker morbidity. The traditional definition of occupational asthma is asthma arising from workplace exposure to airway sensitizing agents, in a previously unsensitized person.[1] A large number of workplace sensitizers have been identified,[2] and the basis of the airway response to these allergens is antibody formation in the at-risk worker. A related mechanism for induction of the allergic response is direct interaction with airway mast cells, with resulting degranulation. Byssinosis is the best known example of this form of occupational asthma. The current Centers for Disease Control surveillance definition of occupational asthma, used in the Sentinel Event Notification System for Occupational Risks program, is broader and more clinical requiring only the demonstration of a relationship between symptoms and ongoing workplace exposures to causative agent(s), independent of sensitization or other specific mechanism.[3]

Recent studies support the concept of such a broader definition of occupational asthma.[4-8] Specifically, this would include asthma that is related to exposure to airway irritants, for which a relationship with the workplace can often be identified, but for which specific immunologic tests are not useful. This approach should take into account the recent growth in recognition of bronchial hyperresponsiveness, either sensitizer or irritant induced, as an important manifestation of occupational asthma.[9]

In 1985, Brooks and associates[4] re-

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ported the development of persistent clinical asthma after one-time, high-level exposures to airway irritants. Since the publication of this case series, additional reports have corroborated their findings.[5-8,12] The etiology, prevalence, and natural history of Reactive Airways Dysfunction Syndrome (RADS), as this syndrome is called, is presently not well understood. The magnitude of risk for RADS after a given exposure is not understood. Preexisting atopy is not believed to be a risk factor for development of this disorder, whereas a history of current cigarette smoking or other predispositions to airway irritation may contribute to its development.[7] Bronchial hyperresponsiveness as demonstrated by nonspecific challenge testing is a hallmark of RADS.[4,7]

A limiting requirement to the concept of RADS, as provided by Brooks and associates,[4] is exposure to a *high* concentration of irritant, resulting in acute upper and/or lower respiratory symptoms ("within 24 hours"). Nevertheless, other investigators have suggested that RADS may follow repeated, low-dose exposures to airway irritants. Tarlo and Broder[7] reported several such cases in their review of occupational asthma referrals, and at least one review has suggested the existence of such cases.[16] Such a "low-dose" RADS phenomenon, if substantiated, may provide an etiologic explanation for some cases of adult-onset asthma, many of which cannot currently be ascribed to classical sensitization mechanisms or more narrowly defined RADS after acute high exposures.[9,16] We report herein the results of a retrospective review of evaluations for asthma that we believe lends further support to the presence of such a phenomenon and suggests the need for prospective evaluation of the risk and risk factors for development of asthma in environments with modest concentrations of respiratory irritants.

Methods

To assess the potential significance of nonacute irritant exposure as an event leading to development of asthma, we reviewed all of the asthma cases referred to our occupational and environmental medicine referral clinic over the 5-year period from July 1986 through July 1991. Evaluations consisted of a complete medical, occupational, and environmental history, physical examination, and, when indicated, diagnostic procedures to confirm the presence of reversible obstructive airway disease. These included assessment of bronchodilator response in the pulmonary function laboratory or response to nonspecific (methacholine) challenge testing. When clinically indicated, methacholine challenge was performed by administration of sequential doses of methacholine at a concentration of 25 mg/mL (maximum of four doses)[14] until a 15% decrease in forced expiratory volume in 1 second, 10% decrease in forced vital capacity, 25% decrease in forced expiratory flow, midexpiratory phase, or 40% decrease in PEFR was observed.[15] Airway constriction was then reversed with inhaled bronchodilator. Positive clinical response to bronchodilator therapy was also considered to be supportive of the diagnosis of asthma in cases where challenge testing was contraindicated or not feasible. Diagnostic confirmation of asthma required the presence of a suggestive clinical presentation and at least one of the following: documentation of reversible airway constriction by pre- and post-bronchodilator spirometry, positive methacholine challenge test demonstrating reversible airway constriction, or positive clinical response to bronchodilator therapy. Documentation of the work-relatedness of asthmatic symptoms was attempted with serial peak flow measurements when the patient was still exposed and able to comply.[17] In the absence of these data, an unambiguous historical association of symptoms with workplace exposures (either irritants or sensitizers) and a confirmed diagnosis of airway hyperreactivity was required for diagnosis of occupational asthma. Bronchial challenge testing with specific agents was not performed. Referral for skin testing was done as clinically indicated and was not performed in any of the cases reported herein. Exposure characterizations including industrial hygiene sampling were available in some cases, and detailed exposure histories were obtained from all subjects. Asthma cases related to both occupational and environmental exposures were considered.

The results of each diagnostic assessment were reviewed to ascertain the proven or suspected cause for each case of occupational asthma. A case was categorized as presumed or suspected classic occupational asthma if exposure to one or more known sensitizing agents was possible, and the onset of asthmatic symptoms was consistent with sensitization (appropriate latency period and/or presence of other allergy symptoms). In the absence of known sensitizing exposures or appropriate latency, and in the event of a known acute exposure to a bronchial irritant preceding the onset of asthma within 24 hours, the case is categorized as RADS.[4] In the absence of both sensitization criteria or RADS criteria, association of development of new-onset adult asthma with a history of repeated exposure to one or more bronchial irritants would place the case in a third and distinct category, low-dose irritant. In addition to this process, each case was specifically reviewed for history of prior presence or treatment for asthma, for presence of smoking and/or respiratory infection concurrent with the onset of asthma, and history of atopy (seasonal allergy, rhinitis, atopic skin disease, or positive immediate hypersensitivity skin test results). Presence of exposure-related symptoms of generalized mucosal irritation (eye, nose, throat) was also ascertained as evidence supportive of the irritant nature of the environment.

Results

Table 1 summarizes the results of this record review according to etiology of each case of asthma. A total of 200 patient records were reviewed. Common diagnoses were asbestosis, silicosis, repetitive motion disorders, peripheral neuropathies, and chemical sensitivity syndrome. Thirty-two cases fulfilled the diagnostic criteria

TABLE 1
Asthmatic Patients Seen in 1986 to 1991

	n	%
Previous diagnosis of asthma	5	16
RADS	7	22
Possible sensitization	6	19
Infection	4	13
Low-dose irritant	10	31
Total	**32**	**100%***

* Does not add up to 100% because of rounding off.

for asthma. Of these 32 cases, 5 had a history of asthma before the exposure of concern, and therefore 27 are considered strictly new adult-onset cases of airway hyperreactivity. Seven represented RADS involving acute exposures to one or more irritants, followed by onset of symptoms within 24 hours. Although in none of the remaining cases was sensitization believed to be the most likely etiology for the exposure-related asthma, for 6 cases, incomplete exposure information or clinical histories prevented satisfactory exclusion of sensitizer-induced asthma, and these are conservatively categorized as possible sensitizations in our tables. Four of the patients had a lower respiratory infection concurrent with onset of asthmatic symptoms, and two of these patients were also cigarette smokers. Both smoking and lower respiratory infection may predispose to or initiate bronchial hyperresponsiveness,[9] and therefore these cases are excluded from further consideration as predominantly irritant induced. Excluding these 22 cases from further consideration results in a final 10 cases, or 31% of asthma in our referral clinic population (37% of new onset), as fulfilling our criteria for low-dose, irritant-induced asthma. None were current smokers and only one had previously smoked (case 3) but had stopped smoking 24 years previously.

Two of the 10 cases who met our criteria for low-dose irritant induction of asthma were still exposed at the time of our evaluation. Both (cases 1 and 2) had a significant drop in PEFR at work compared with nonwork values. This was confirmed in both by preshift to postshift decline in forced expiratory volume in 1 second. None of the other exposures were ongoing at the time of our evaluations, although all 8 patients had persistent asthmatic symptoms, triggered and/or exacerbated by multiple environmental irritants.

Cases 3, 4, 5, and 7 were all exposed to fumes from waste acid drums and other irritants at an abandoned fire retardant manufacture site. Case 3 was a fire inspector who developed increasing symptoms after each of a series of three visits ranging from 1 hour to half a day at the site. He had no history of respiratory symptoms or clinically apparent firefighting injury and had been an inspector for the previous 4 years. After blood-tinged sputum appeared 4 months after cessation of exposure, his personal physician performed bronchoscopy and reported only generalized mucosal inflammation. Treatment with inhaled and oral steroids did not significantly ameliorate his symptoms. Cases 4, 5, and 7 were federal employee hazardous waste remediation investigators and site planners who became involved in the same site many months later, but on a daily basis. All three had asthma symptoms within a week of arrival on site.

Case six involved exposure to cutting oils, and while there are conceivable sensitizers in these as well as in cases 8, 9 and 10, the clinical presentation was much more of reactivity to many irritants rather than to a specific agent, ie, symptoms were worst at work but significantly troublesome in many other settings.

Eleven of 27 (41%) adult-onset asthma patients met our criteria for a history of atopy preceding onset of asthma. This is similar to the 4 of the 10 (40%) cases that we categorize as having low-dose, irritant-induced asthma who met our criteria for atopy. The absence of a clinical course consistent with sensitization, the absence of exposure to known sensitizers, and the widespread triggers of their subsequent symptoms allowed us to eliminate satisfactorily the possibility of specific allergen-induced asthma in these patients. We could not identify specific agents with which to reasonably attempt immediate hypersensitivity skin tests. All 6 low-dose exposure patients who underwent methacholine challenge had positive tests, consistent with the diagnosis of asthma, lending further support to the diagnosis of irritant-induced asthma in these patients.

Table 2 provides additional information on the patients in the low-dose irritant-exposed group. The information concerning diagnostic criteria for asthma indicates that 9 of the 10 cases had positive methacholine challenge and/or positive bronchodilator response on spirometry. The remaining case had an excellent clinical response to bronchodilators.

Discussion

This review of asthma referrals to our occupational and environmental medicine clinic suggests a divergence between the classical approach to occupational asthma and the reality of current occupational medicine practice. Although much has been written about sensitizer-induced asthma, it is only relatively recently that irritant-induced asthma has been recognized formally. The results of this case review indicate that in addition to the RADS phenomenon, where asthma follows acute exposure to respiratory irritants, there may exist a form of occupational asthma wherein symptoms follow repetitive, low-dose exposures to respiratory irritants. The diagnosis of irritant-induced asthma in these 10 patients is supported by the presence of nonspecific bronchial hyperresponsiveness in all cases, and the presence of exposure-associated generalized mucosal irritation symptoms in most cases. If the asthma experience of our clinic is similar to that of other occupational practices, then the prevalence of this form of exposure-related asthma may indeed be significant. Tarlo and Broder[7] observed a similar nonacute RADS phenomenon in their case series. In contrast to their study, we did not confirm the presence of sensitizer-induced asthma in any of our patients, although one patient did have sensitizer-induced hypersensitivity pneu-

TABLE 2
Low-Dose Irritant Exposure Group

Case	Age at Onset, y	Sex	BHR Criteria*	Irritant	Exposure Frequency	Symptoms of Mucosal Irritation	Exposure Duration	Still Exposed?
1	47	M	PFT†‡ w/ BD	Bisulfite and SO_2	Daily	Yes	3 y	Yes
2	59	F	MCT†‡	Chemistry teaching laboratory	Daily	Yes	4 y	Yes
3	52	M	MCT	Acid mist	Few	Yes	4 mo	No
4	53	M	MCT	Acid mist	Daily	No	4 mo	No
5	34	F	MCT	Acid mist	Daily	Yes	4 mo	No
6	44	M	MCT	Cutting oil	Daily	Yes	7 y	No
7	33	F	MCT	Acid mist	Daily	Yes	4 mo	No
8	28	F	BD clin	Cleaning agents	Daily	Yes	2 y	No
9	37	F	PFT w/BD	Perfume agents in research laboratory	Daily	Yes	2 mo	No
10	23	F	PFT w/BD	New carpet installation	Daily	No	3 mo	No

Age at onset and sex are indicated, as is the specific diagnostic criterion for airway hyperreactivity in each case. Also provided is the nature of the irritant, exposure frequency, an entry concerning presence or absence of symptoms of generalized mucosal irritation, the duration of exposure before presentation, and an entry indicating whether there was continued exposure to the inciting irritant at the time of initial evaluation.

* BHR, bronchial hyperresponsiveness; PFT, pulmonary function test; BD, bronchodilator; BD clin, clinical response to bronchodilator; MCT, methacholine challenge test.

† Portable peak expiratory flows significantly lower when exposed than on control days.

‡ Pre- and postshift spirometry showed significant cross-shift drop.

monitis and we have subsequently seen such sensitization cases of asthma. We both observed a similar percentage of acute RADS phenomena among occupational asthma cases.

The etiology of irritant-induced asthma remains unknown. Although we have chosen to distinguish between acute and nonacute irritant-induced asthma based on exposure history, we do not know whether there is an underlying pathophysiologic difference between these two distinct clinical presentations. Positive methacholine challenge results appear to be a shared diagnostic finding for these two syndromes, suggesting that airway inflammation, with resulting nonspecific bronchial hyperresponsiveness, may be common to both. It has been proposed that respiratory irritants may act as potentiators of nonspecific bronchial hyperresponsiveness through induction of airway inflammation or by other mechanisms.[9,10] Individual factors predisposing to the development of persistent bronchial hyperresponsiveness after exposure have not been identified but cigarette smoking has been suggested to play a role.[13] Although atopy could be a risk factor, the comparable rates among our low-dose cases and our asthma cases as a whole does not suggest that it is. Future studies should include a standardized assessment of allergic diathesis. Because bronchial hyperresponsiveness may result from respiratory infection,[11] we excluded patients with a recent history of a clinically apparent infection from our low-dose exposure category.

The results of this case review and the findings of other investigators suggest an association between recurrent low-dose irritant exposure and development of adult-onset asthma. Analytic, preferably prospective, studies are needed to examine the significance of this association for development of occupational asthma. Determination of the pathophysiologic mechanisms underlying this disorder may lead to identification of preventive measures and specific treatment modalities, enabling a reduction in the morbidity associated with this potentially significant form of adult-onset asthma.

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Income	Zip	Town, State	Households
$226,829	60082	Techny, IL	119
142,217	94027	Menlo Park, CA	2,294
134,896	07046	Mountain Lakes, NJ	1,408
132,656	60043	Kenilworth, IL	843
132,593	10506	Bedford, NY	1,860

From "42,496 Secrets are Bared," by A. E. Serwer in *Fortune*, January 24, 1994, p 130.