

Occupational asthma secondary to enzymes used in cheese production

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ABSTRACT

Occupational asthma (OA) accounts for 5–10% of all asthma in adults. Although OA secondary to enzymes has been reported, it is rare in the context of food preparation. In the cheese production industry, multiple powdered enzymes are used to soften and flavor cheese. Work-related asthma secondary to enzymes used in this manner has not been previously reported. We present two cases of OA after exposure to airborne enzyme powders used in cheese production. Both patients were adult women without histories of asthma who worked in a facility that used fungal and pancreatic-based enzymes to soften and flavor cheese. Both developed asthma symptoms within 1 year of employment and experienced relief of symptoms away from work. One patient had occupational rhinitis. Each underwent allergy skin testing, chest radiograph, pulmonary function testing, and methacholine challenge. Both patients had markedly positive skin tests to multiple enzyme antigens used at work. Spirometry, lung volumes, and chest radiographs were normal for both patients when they were asymptomatic and had implemented avoidance measures. Methacholine challenge was positive in one patient ($PC_{20} = 0.13$ mg/mL). Both workers took appropriate respiratory protection measures during powder exposure and their symptoms improved. Enzyme powder used in cheese production is a trigger for OA.

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Occupational asthma (OA) is the most prevalent form of occupational lung disease, accounting for 25% of all cases¹ and 5–10% of all asthma in adults.² Although OA secondary to enzymes has been reported,^{3,4} it is rare in the context of food preparation. In the cheese production industry, multiple powdered enzymes, derived from fungal and animal sources, are used to soften and flavor the cheese. We present two cases of OA after exposure and sensitization to airborne enzyme powders used in cheese production, etiologic agents that have not been previously reported.

CASES

Patient 1

Patient 1 was a 34-year-old woman who developed wheezing, coughing, and shortness of breath 1 year after beginning work at a local cheese processing plant. Her symptoms also included rhinorrhea, sneezing, oc-

ular erythema, and occasional urticaria that began at the same time. Her job included mixing various powdered enzymes into a liquid form that would later be used to soften and flavor cheese. The patient was exposed to these powdered enzymes on a daily basis. She did not work in a negative-pressure hood and did not wear personal respiratory protection. Her symptoms would occur rapidly on exposure to the enzymes and dramatically improved on weekends and while on vacation. On three occasions the patient had to leave the mixing laboratory secondary to respiratory distress. She regularly used a short-acting bronchodilator 10–15 times during an 8-hour shift. The patient had no history of asthma. However, she had allergic rhinitis and had known sensitivity to multiple allergens including cat dander and multiple pollens but not to mold. She had a 10-pack-year history of smoking.

Patient 2

Patient 2 was a 42-year-old woman with no history of asthma. She developed cough and dyspnea within 1 year of employment at the same plant. She denied having rhinitis symptoms at work, but had a history of allergic rhinitis. Her job was similar to patient 1 and she was exposed to airborne powdered enzymes daily. She did not consistently use personal respiratory protection. Her symptoms improved away from the workplace on weekends and immediately returned on reexposure to the enzymes. She reported partial or limited relief from short-acting bronchodilators while at work.

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Table 1 Percutaneous skin test results for each patient with enzymes used in the plant

Antigen	Patient 1	Patient 2
<i>Aspergillus oryzae</i>	Negative	4+
Porcine pancreas	4+	4+
<i>Rhizopus oryzae</i>	Negative	2+
<i>Penicillium roqueforti</i>	3+	1+
<i>Candida rugosa</i>	4+	2+
Mixed fungal	4+	Negative
Calf glandular tissue	Negative	1+

She had no history of smoking. At the time of visit to our clinic, she had been removed from the enzyme mixing laboratory for several years and reported dramatic improvement of her symptoms. Although only these 2 workers presented for further evaluation, both patients indicated that at least 30 other workers at the plant had respiratory symptoms at work.

RESULTS

The seven most common antigens in the enzyme mixture were obtained in powdered form and diluted with 0.9% normal saline to a concentration of 10 mg/mL. These antigens included fungal enzymes—*Aspergillus oryzae*, *Penicillium roqueforti*, *Candida rugosa*, mixed fungal, and *Rhizopus oryzae*—and animal-derived enzymes—porcine pancreas and calf glandular tissue. Percutaneous skin testing was performed using Quintip devices (Hollister-Stier, Spokane, WA) (Table 1). Histamine phosphate (10 mg/mL) and sterile 0.9% saline were used as positive and negative controls, respectively. A wheal greater than the negative control 20 minutes after puncture was considered a positive response. Grading of skin tests from 1+ to 4+ was according to increasing wheal size. Patient 1 was sensitive to *P. roqueforti*, *C. rugosa*, mixed fungal, and porcine pancreas extracts. Patient 2 was sensitive to all of the antigens except mixed fungal antigen. Skin testing was also performed to common aeroallergens. Patient 1 was sensitive to ragweed and grass pollen, and cat and dog dander. Patient 2 was sensitive only to tree pollen.

Complete blood counts were normal in both patients. Total serum IgE was elevated (918 IU/mL) in patient 1 but was normal in patient 2. Spirometry and chest radiographs showed no significant abnormalities in either patient. Methacholine challenge for patient 1 revealed significant bronchial hyperresponsiveness (BHR) with a PC₂₀ of 1.3 mg/dL. Patient 2 had minimal BHR, with a PC₂₀ of 13 mg/dL. However, the challenge for patient 2 was performed several years after avoidance measures had been established at the plant.

Patient 1 was started on daily inhaled corticosteroids and was removed from direct exposure to the enzymes. Patient 2 was advised to continue avoidance. Each patient was instructed to wear a dual canister personal respirator while in the workplace. The company also installed more efficient ventilation systems throughout the plant. These avoidance measures resulted in dramatic improvement of symptoms in patient 1 and allowed for rapid weaning of the inhaled corticosteroids. Both patients are currently doing well with no pharmacologic treatment. The plant has since closed and moved to another state. To our knowledge, this decision to relocate was unrelated to the health affects to the workers.

DISCUSSION

We present two workers who experienced OA related to enzymes used in cheese processing. Enzymes are high molecular weight antigens used in various industrial processes. They were first used commercially in the United States in 1967 for detergent production.³ Since then, they have been used in several other industries including pharmaceutical manufacturing, dry cleaning, and food preparation.⁴

OA secondary to enzymes was first described by Flindt and Pepys in 1969 after several workers in a detergent plant developed respiratory symptoms from exposure to alcalase, a *Bacillus subtilis*-derived enzyme.^{5,6} The authors showed positive skin tests to the enzyme in most of the workers and inhalation challenges induced dual airway responses in several subjects. Epidemiologic surveys performed in the 1970s determined that workers exposed to *B. subtilis*-derived enzymes became sensitized at a rate of 20–60%.⁷ Since that time, OA secondary to numerous other enzymes, both fungal and animal derived, have been reported.⁴

OA secondary to enzyme exposure in food preparation has been described in bakers and egg processors. Enzymes in baker's yeast can trigger baker's asthma, one of the most common forms of OA. Amylase enzymes derived from *A. oryzae* (one of the antigens in our cases) are used to improve the rising of dough and the quality of the bread. In a cohort study, 35 of 118 bakery workers had asthma and/or rhinitis symptoms after exposure to flour.⁸ Twelve of these 35 patients had specific IgE to *Aspergillus*-derived amylase based on radioallergosorbent testing. Other studies have confirmed the importance of enzymes as antigens in baker's asthma.^{9,10}

OA was reported in a worker exposed to enzymes in an egg processing plant.¹¹ The worker developed respiratory symptoms after daily exposure to airborne hen egg-white-derived lysozyme. Sensitivity to the lysozyme was confirmed by skin testing, serum IgE antibodies, and specific bronchoprovocation with lysozyme inducing significant airflow obstruction.

The diagnosis of OA begins with a detailed clinical and occupational history. This should include duration of symptoms and employment, evaluation of symptoms away from work, potential antigen exposures, and workplace conditions.¹² Both of our patients had histories consistent with OA. They each had significant exposure to multiple airborne allergens without respiratory protection. They also had relief of symptoms away from the workplace and after avoidance measures were implemented.

It is important to evaluate other risk factors for OA, including prior atopic disease and smoking history. Studies have indicated an increased rate of sensitization to enzymes in atopic workers compared with nonatopic workers.^{13,14} One study showed an increase in OA in atopic patients exposed to enzymes, although this data has not been consistently replicated.¹⁵ Although neither of our patients had a history of asthma, both had allergic rhinitis. One of our patients also had a history of smoking. Cigarette smoking is a potential predisposing and aggravating factor in the development of OA. Flood *et al.* showed cigarette smokers to be several times more likely to develop OA secondary to enzymes.¹⁶ Race, gender, and age are not considered risk factors for enzyme-induced OA.^{13,14}

Diagnosis of enzyme-induced OA includes percutaneous skin testing to the enzyme antigens in question as well as seasonal and perennial aeroallergens. One study, using specific bronchial challenge as the gold standard, showed enzyme-specific skin testing was 100% sensitive and 93% specific. In comparison, IgE radioallergosorbent testing yielded a sensitivity of 62% and specificity of 96%.¹⁷ Both of our patients showed significant skin hypersensitivity to multiple antigens used in the plant. In addition to skin testing, lung function testing and BHR should be evaluated. Although antigen-specific inhalation challenge is considered the gold standard, it is often impractical and potentially unsafe.¹⁸ Additional evidence of workplace asthma includes cross-shift peak flows to assess for declines in peak expiratory flow measurements before and after antigen exposure. If possible, more complete pulmonary function testing could be performed before and after exposure at work. In our patients, specific inhalation challenges were declined by each patient. Pulmonary function testing was normal and methacholine provocation testing was positive in patient 1 but borderline in patient 2. Methacholine sensitivity can return to normal after avoidance of the inciting antigen.¹⁹

The most effective treatment of OA is avoidance of the offending agent. This may include relocating the worker to a different area of the plant or installing more efficient ventilation systems. Utilization of approved respirators may also be helpful. Several studies have shown reduction of skin reactivity and clinical

symptoms when appropriate avoidance has been used by workers.^{20,21} Both of our patients reported rapid resolution of their symptoms when the enzymes were mixed in a separate laboratory and appropriate respiratory protection was used. Improved ventilation systems in the plant were also effective in reducing their symptoms.

Pharmacologic treatment may also be necessary but should not be considered replacement for avoidance measures. Inhaled corticosteroids may be useful while methods to reduce exposure are being initiated or in patients who show symptoms after avoidance is implemented. Although patient 1 initially required pharmacologic therapy, it was quickly weaned after avoidance measures were incorporated at the plant. At this time, both patients have sought employment where enzymes are not used. They are healthy and require no medications.

CONCLUSION

We report two workers who developed OA to enzyme powders used in cheese production. This represents a new OA with a known enzyme to be included in the expanding list of occupational allergens.

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REFERENCES

1. Ross DJ, Keynes HL, and McDonald JC. SWORD '97: Surveillance of work-related and occupational respiratory disease in the UK. *Occup Med (Lond)* 48:481–485, 1998.
2. Kogevinas M, Anto JM, Sunyer J, et al. Occupational asthma in Europe and other industrialized areas: A population based study. *Lancet* 353:1750–1754, 1999.
3. Bernstein IL. Enzyme allergy in populations exposed to long term, low level concentrations of household laundry products. *J Allergy Clin Immunol* 49:219–237, 1972.
4. Bernstein DI, and Melo JL. High molecular weight agents. In *Asthma in the Workplace*, 2nd ed. Bernstein IL, Chan-Yeung M, Malo JL, and Bernstein DI (eds.). New York: Marcel Dekker, Inc., 363–375, 1999.
5. Flindt MLH. Pulmonary disease due to inhalation of derivatives of *Bacillus subtilis* containing proteolytic enzymes. *Lancet* 1177–1181, 1969.
6. Pepys J, Longbottom JL, Hargreave FE, and Faux J. Allergic reactions of the lungs to enzymes of *Bacillus subtilis*. *Lancet* 7607:1181–1184, 1969.
7. Belin L, Hoborn J, Falsen E, and Andre J. Enzyme sensitization in consumers of enzyme-containing washing powder. *Lancet* 7684:1153–1157, 1970.
8. Bauer X, Fruhmman G, Haug B, et al. Role of *Aspergillus* amylase in baker's asthma. *Lancet* 8471:43, 1986.
9. Bauer X, Fruhmman G, and Weiss W. Baking additives as new allergens in baker's asthma. *Respiration* 54:70–72, 1988.
10. Quirce S, Cuevas M, Diez-Gomez M, et al. Respiratory allergy to *Aspergillus*-derived enzymes in baker's asthma. *J Allergy Clin Immunol* 90:970–978, 1992.
11. Bernstein JA, Kraut A, Bernstein DI, et al. Occupational asthma induced by inhaled egg lysozyme. *Chest* 103:532–535, 1993.

12. Bardana EJ Jr. Occupational asthma. *J Allergy Clin Immunol* 121:S408–S411, 2008.
13. Newhouse ML, Tagg B, and Pocock SJ. An epidemiologic study of workers producing enzyme washing powders. *Lancet* 7649: 689–693, 1970.
14. Gandevia B, and Mitchell C. The dangers of proteolytic enzymes to workers. *Med J Aust* 19:1032–1033, 1971.
15. Juniper CP, and Roberts DM. Enzyme asthma: 14 years' clinical experience of a recently described disease. *J Soc Occup Med* 34:127–132, 1984.
16. Flood DGS, Blofeld RE, Bruce CF, et al. Lung function, atopy, specific hypersensitivity, and smoking of workers in the enzyme detergent industry over 11 years. *Br J Ind Med* 42:43–50, 1985.
17. Merget R, Stollfus J, Wiewrodt R, et al. Diagnostic tests in enzyme allergy. *J Allergy Clin Immunol* 92:264–277, 1993.
18. Cartier A, Bernstein IL, Burge PS, et al. Guidelines for broncho-provocation on the investigation of occupational asthma. *J Allergy Clin Immunol* 84:823–829, 1989.
19. Butcher BT, O'Neil CE, Reed MA, et al. Development and loss of toluene diisocyanate (TDI) reactivity: Immunologic, pharmacologic and provocative inhalation challenge studies. *J Allergy Clin Immunol* 70:231–235, 1982.
20. Chan-Yeung M, Maclean L, and Paggiaro PL. Follow-up study of 232 patients with occupational asthma caused by western red cedar. *J Allergy Clin Immunol* 79:792–796, 1987.
21. Moller DR, Brooks SM, McKay RT, et al. Chronic asthma due to toluene diisocyanate. *Chest* 90:494–499, 1986. □

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