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Letter

Occupational allergic respiratory disease due to royal jelly

Royal jelly (RJ) is a secretion of the hypopharyngeal and mandibular glands of worker honeybees (*Apis mellifera*). RJ has been used as a health supplement worldwide at any age because it has been found to have several beneficial properties.^{1,2}

Honey and RJ are complex heterogeneous mixtures of flower nectars, sugars, proteins, and the glandular secretions of honeybees.³ Approximately one half of its dry weight consists of proteins; other components are fatty acids, sugars, and vitamins.¹

We report on 2 cases of occupational allergic respiratory disease from the inhalation of RJ.

The first patient was a 31-year-old man with a history of allergic rhinoconjunctivitis to pollens who was employed in a pharmacy laboratory for 4 years. He developed work-related bronchial, nasal, and ocular symptoms, such as itching, watery eyes, sneezing, nasal stuffiness, and rhinorrhea, during the previous 2 years. These symptoms markedly decreased when away from work and worsened while at work. One year before referral to our clinic, he began to have dry cough and breathlessness, which he attributed to his work environment. Upper and lower respiratory tract symptoms were present only on the days that he handled RJ at work. He had no reactions to foods but he did not remember eating honey.

The allergy study showed the following results: skin prick test (SPT) results were positive for grass (8-mm mean wheal diameter) and *Dermatophagoides farinae* (3 mm) and were negative for olive pollen, moulds, other mites, and animal dander. SPT test results with a homemade RJ extract (10% wt/vol) were positive (5.5 mm). Prick-prick test results with natural honey also were positive (4.5 mm), with a histamine control SPT of 6 mm. Three atopic subjects underwent prick testing with RJ and showed negative results.

Serologic tests yielded a total serum immunoglobulin E (IgE) level of 196 kU/L and specific IgE (ImmunoCAP, ThermoFisher, Uppsala, Sweden) levels of 2 kU/L to *Lolium* species, 1.4 kU/L to *Dermatophagoides pteronyssinus*, 4.7 kU/L to honey, and 1.7 kU/L to *A. mellifera*.

Spirometry showed a forced vital capacity (FVC) of 5.1 L (95%), force expiration volume in 1 second (FEV₁) of 4.3 L (94%), and a FEV₁/FVC ratio of 84%.

A methacholine inhalation test was performed according to an abbreviated protocol,⁴ and the results were expressed as the provocation concentration of methacholine (milligrams) that caused a decrease in FEV₁ of 20%. This test result was positive (0.92 mg of cumulative dose) when the patient was working and negative 6 months away from work.

Specific inhalation challenge testing was carried out in the hospital laboratory by tipping RJ powder from one tray to another for 5 minutes. Spirometry was performed at baseline and at 2, 5, 10, 15, 20, 30, 45, and 60 minutes after the challenge with RJ. After the first 2 minutes, the patient began to exhibit symptoms of

rhinoconjunctivitis. A 21% decrease in FEV₁ compared with baseline values was observed 5 minutes after exposure to RJ. Peak expiratory flow (PEF) was measured at baseline and then hourly (except during sleep) for 24 hours after the specific challenge. A 22% decrease in PEF was detected 5 hours after the challenge test. A control challenge day was performed by exposing the patient to a control substance (saline), and no changes in FEV₁ were observed.

The second patient was a 22 year-old man with a family history of atopy but no history of pollen allergy who worked in a pharmacy laboratory for 4 months. He complained of bronchial, nasal, and ocular symptoms, such as cough, breathlessness, itching, watery

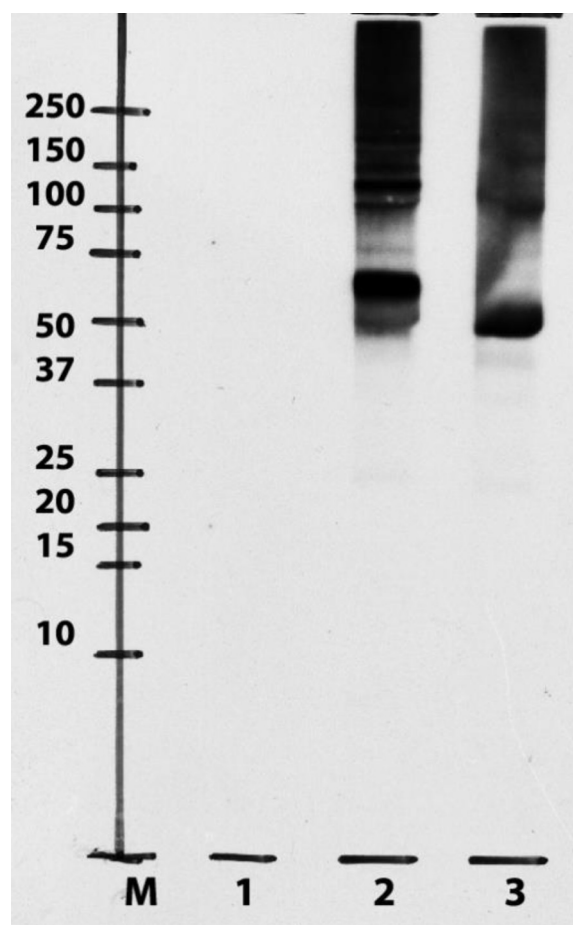


Figure 1. Royal jelly immunoblots. Lane 1, royal jelly extract and negative control; lane 2, royal jelly extract and sera from patient 1; lane 3, royal jelly extract and sera from patient 2. M, molecular weight markers (10, 15, 20, 25, 37, 50, 75, 100, 150, and 250 kDa).

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eyes, sneezing, nasal stuffiness, and rhinorrhea, 3 months after he started working in the laboratory. These symptoms markedly decreased when he was away from work and worsened while at work. Upper and lower respiratory tract symptoms were present only on the days that he handled RJ and honey in his workplace. The patient tolerated the intake of honey.

The allergy study showed negative SPT results to grass, olive, mites, molds, and animal dander. Results of an SPT with a home-made RJ extract (10% wt/vol) were positive (5 mm), as were those with a prick-prick test with natural honey (4.5 mm). The histamine control SPT wheal was 5.6 mm.

Spirometry showed an FVC of 4.82 L (93%), FEV₁ of 3.7 L (85%), and FEV₁/FVC ratio of 78%. The bronchodilator test result was positive (15% improvement and >200 mL).

The serologic tests yielded a total serum IgE level of 30 kU/L, and specific IgE (ImmunoCAP) test results for *Phleum* species, *Olea europaea*, *Artemisia vulgaris*, and *A mellifera* were negative; the specific IgE level for honey was 4.7 kU/L. The eosinophil cationic protein level was 30 µg/L.

Serial measurements of PEF showed a variability of 34% while working.

The patient did not give his informed consent for the bronchial challenge test with RJ.

Sodium dodecyl sulfate polyacrylamide gel electrophoresis immunoblot analysis with RJ extract was performed according to the Laemmle method in the 2 patients.⁵ Reactive bands with the ability to bind IgE were detected in the 2 sera samples; the molecular weight of these bands was 45 to 150 kD, with a remarkable band at 45 to 50 kDa and another of 55 kDa (Fig 1).

Royal jelly has been implicated as an allergen in mild reactions,² such as oral allergy syndrome,⁶ and severe reactions, such as anaphylaxis⁷ and asthma.⁸ They can occur in children^{1,6} and adults⁷ and usually after eating an RJ food supplement.

No cases of asthma and rhinoconjunctivitis by RJ inhalation have been described in the literature. The present patients had occupational asthma and rhinoconjunctivitis, because they had the symptoms only at work, and patient 1 had a positive specific challenge test reaction to RJ and patient 2 showed high variability in PEF while working.

Patient 1 was sensitized to mites, probably owing to cross-reactivity, because *D pteronyssinus* and RJ have been found to share common epitopes.¹ Most of the patients allergic to RJ exhibit positive SPT reactions to pollens, especially of the Compositae family.¹ Surprisingly, patient 2 was not sensitized to any pollen. In contrast, most patients react to ingested or inhaled RJ after being

sensitized by inhaled pollens. This sensitization would explain why patients can react after the first intake of RJ.¹

The molecular results of these patients are in accord with several studies that have reported that patients sensitive to RJ possess IgE binding proteins of 40 to 55 kD that have been recognized as the major allergens of RJ^{2,9} (Fig 1). Therefore, although patient 1 was sensitized to grass pollen, the 2 patients likely were primarily sensitized to RJ in the workplace because they exhibited the same pattern of sensitization, they needed a latency period after being exposed to RJ to manifest their symptoms, and patient 2 showed no other sensitization, except to honey, which he tolerated.

To our knowledge, these are the first 2 cases of occupational allergic respiratory disease from the inhalation of RJ.

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