Anaphylaxis Due to Methylprednisolone

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Key words: Methylprednisolone. Corticosteroids. Intradermal skin test. Anaphylaxis. Hypersensitivity.

Palabras clave: Metilprednisolona. Corticosteroides. Prueba cutánea intradérmica. Anafilaxia. Hipersensibilidad.

Corticosteroids are widely used in the treatment of a large number of diseases, because of their efficacy as anti-inflammatory and immunosuppressive agents. The most frequent allergic reaction to corticosteroids is allergic contact dermatitis, occurring in 2.9%-4.1% of cases [1]. Adverse reactions due to corticosteroid hypersensitivity, including anaphylaxis (first described in 1974 [2]), angioedema [3], urticaria, generalized cutaneous eruption, and severe bronchospasm [4] occur in 0.3% in cases involving systemic administration [1]. Although anaphylaxis is not a frequent adverse effect of corticosteroid treatment, its diagnosis is very important due to the widespread use of these drugs in a variety of diseases [1,2,4-6].

A 32-year-old woman undergoing immunotherapy for treatment of allergic seasonal rhinoconjunctivitis and asthma due to pollen sensitization, suffered from ocular pruritus, lacrimation, conjunctival erythema, chest tightness, and shortness of breath 60-90 minutes after her last vaccine dose. She was admitted to the emergency department and treated with parenteral methylprednisolone hemisuccinate. Fifteen minutes later, she experienced cutaneous pruritus and generalized erythema, and her asthma attack worsened.

Three years later, she was referred to our department for assessment. Skin prick tests were performed with a panel of aeroallergens, and positive reactions were observed exclusively to pollens.

Intradermal skin test (IST) with methylprednisolone (10 mg/mL) was negative at 20 and 60 minutes. As hypersensitivity due to corticosteroids is not frequent, we decided to do a challenge test the same day to confirm whether methylprednisolone was tolerated by the patient. Intramuscular challenge was carried out with 10 mg of methylprednisolone hemisuccinate. Ten minutes later, she experienced pruritus in the pharynx, eyes, and nose, dry cough, and hives on both arms. Furthermore, having performed IST 90 minutes earlier, a reaction was observed that grew to 15×20 mm. The patient was treated with intramuscular epinephrin.

Based on these observations, we decided to determine whether any other corticosteroids could be tolerated. Accordingly, we carried out ISTs with betamethasone (4 mg/mL), hydrocortisone (10 mg/mL), triamcinolone (20 mg/mL), and paramethasone (20 mg/mL), with negative results in all cases. Intramuscular challenge was performed with betamethasone (4 mg), hydrocortisone (200 mg), and paramethasone (40 mg), all of which yielded negative results. Controlled oral challenges were carried out with prednisone (30 mg) and deflazacort (30 mg), again with negative results. Excipients (monosodium and disodium phosphate) were excluded because they had been tolerated by the patient in other drugs.

Comaish [7] described a patient who had episodes of hives after oral and intra-articular corticosteroids, and IST was positive at 3 hours or later for prednisolone acetate, prednisone, and hydrocortisone. Our patient's IST was probably negative at the beginning due to the immunosuppressant effect of corticosteroids. The drugs would inhibit the effect of immunoglobulin (Ig) E on mast cells and the release of cytokines, leading to negative or delayed response in cutaneous tests [8]. We therefore suggest that it would be useful to do another test with a reading at 90 minutes.

We may also speculate that the amount of methylprednisolone hemisuccinate used for IST was so small that its capacity to efficiently bind arginine and guanidine groups on human serum albumin was lost [2,9]. The intramuscular challenge provided higher levels of hemisuccinate, which would lead to the formation of steroid-protein conjugates in plasma or skin, thereby converting the steroid hapten into a complete antigen and allowing the steroid molecule to be presented to the immune cells and provoking a positive IST result [9,10].

In conclusion, we describe a case of IgE-mediated anaphylaxis due to methylprednisolone, confirmed by IST and intramuscular challenge. Our results indicate that it would be useful to read IST results at 90 minutes to detect a possible immunosuppressant effect and perhaps to increase the amount of methylprednisolone hemisuccinate used. Patients should be tested with other steroid preparations to identify a corticosteroid that could be used therapeutically.

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Exposure of Grass Pollen to Volatile Organic Compounds Enhances Skin Prick Test Reactivity

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Key words: Grass pollen. Volatile organic compounds. Sulfur dioxide. Laser Doppler imaging.

Palabras clave: Polen de gramíneas. Componentes orgánicos volátiles. Dióxido sulfúrico. Imagen láser dopler.

Air pollution as a result of the combustion of fossil fuels is considered to be an important factor promoting the increase in allergic airway diseases [1,2]. In addition to effects on the respiratory system in asthmatics, traffic-related pollutants have been shown to interact directly with pollen grains, enhancing the release of pollen-associated lipid mediators (PALMs) in vitro [3]. PALMs are bioactive lipid mediators with similarities to leukotrienes (proinflammatory $PALM_{LTB4}$) and prostaglandins (immunomodulatory $PALM_{PGE2}$) liberated by pollen [4].

The aim of this study was to investigate the effect of volatile organic compounds (VOCs), sulfur dioxide (SO_2), and synthetic air on grass pollen (*Phleum pratense* L.) allergenicity as measured in vivo by skin prick tests (SPT) in patients with grass pollen allergy using microdialysis and laser Doppler imaging.

Pollen samples were exposed for 18 hours at 50% relative humidity to the VOCs toluene/m-xylene (1:3; 125 mg/m^3), SO_2 (13 mg/m^3), or synthetic air in a specially constructed exposure chamber [5]. Concentrations of both toluene/m-xylene and SO_2 exceeding the levels in heavily polluted urban areas were chosen to represent a worst case scenario [6,7]. The exposure levels used in the study were selected based on occupational exposure limits for the substances in Germany (MAK values) [8]. For toluene/m-xylene the concentration was chosen to be 5-fold lower than the MAK value and, thus, frequently encountered in the workplace environment, while the SO_2 concentration was 10-fold higher, to represent heavy air pollution previously prevalent in the vicinity of industrial combustion processes in Eastern Europe [8]. The exposure chamber operates as a fluidized bed reactor and allows exposure of pollen to gaseous pollutants under airborne "physiological" conditions in a dose-dependent and time-dependent fashion [3].

After exposure of the pollen to VOCs, SO_2, or synthetic air, aqueous extracts were prepared (10 mg/mL pollen) and Phl p 5 and PALMs were measured by enzyme-linked immunosorbent assay. In the extracts, the substances Phl p 5, $PALM_{PGE2}$, and $PALM_{LTB4}$ were measurable at the following concentrations after exposure to VOCs, SO_2, and synthetic air: Phl p 5 (36.9 µg/mL, 19.03 µg/mL, and 31.9 µg/mL, respectively), $PALM_{PGE2}$ (685.8 pg/mL, 612.8 pg/mL, and 421.6 pg/mL, respectively), and $PALM_{LTB4}$ (285.7 pg/ml, 1097.2 pg/mL, and 191.7 pg/mL, respectively). In addition, pollen grains were analyzed by light microscopy and no changes were detected after exposure.

Subsequently, skin prick tests were performed on the volar surface of the forearms with these extracts in 10 patients with allergic rhinoconjunctivitis to grass pollen (7 female, 3 male; mean [SD] age, 28.6 [6.3] years). At each test field, microdialysis probes were implanted and total protein and tryptase content were measured [9]. Additionally, the blood flow in the area of the SPT was recorded every 15 minutes by laser Doppler imaging (Moor Instruments, Axminster, Devon, UK) [9]. Since the skin blood-flow data showed a log normal distribution, further analysis was performed after log transformation of the data. The variable used for analysis was the difference in reaction between the exposure condition and the corresponding control condition at an equivalent time point.

Skin blood flow was significantly enhanced by extracts of toluene/m-xylene-exposed pollen 60 minutes after SPT ($P < .05$; Figure). No such effect was seen for SO_2 exposure or for protein content and tryptase in the microdialysate.

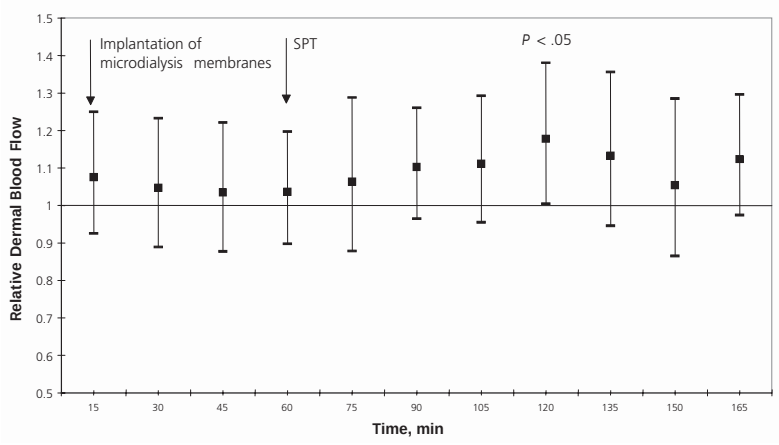

Figure. Increase in relative skin blood flow after skin prick test with grass pollen extracts exposed to toluene/m-xylene (125 mg/m^3) compared to extracts from grass pollen exposed to synthetic air in 10 patients with grass pollen allergy. Skin blood flow was increased significantly compared to control 60 minutes after skin prick test (+17.8%; 95% confidence interval, 0.5% – 38.1%; $P < .05$). Data are shown as geometric means of relative change; whiskers show 95% confidence interval.

In this study, pollen exposed to VOCs released elevated levels of Phl p 5 and PALMs, and led to an increased skin blood flow after SPT. Taking into consideration the capacity of VOCs to disturb membranes [10], exposure to toluene/m-xylene may lead to impairment of the pollen exine and intine and subsequently to increased release of the aforementioned substances. Our results indicate a possible enhancement of the inflammatory potency of pollen after VOC exposure and support the concept that adjuvant factors from the human environment might contribute to the manifestation of allergic diseases.

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An Extremely Painful Fracture of the Metacarpus

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Key words: Plaster. Contact dermatitis. Colophony.

Palabras clave: Vendaje. Dermatitis de contacto. Colofonia.

Contact dermatitis is a common skin problem and includes all adverse cutaneous reactions (immunologic or not) that result from direct contact between an exogenous agent and the surface of the skin [1]. Today, there are more than 85 000 chemicals in the world and almost any substance can be an irritant. More than 3 700 substances have been identified as contact allergens.

Although contact dermatitis is rare during the first years of life, its incidence increases in teenagers, mainly because of fashion trends such as body piercing, henna tattoos, cosmetics, and skin painting.

We report the case of an 11-year-old girl who attended the emergency room with pain in her right hand after an accidental fall. She was diagnosed with fracture of the fifth metacarpal bone and her hand was immobilized with a plaster cast. She returned to the emergency room 48 hours later complaining of increased pain. The orthopedic surgeon refused to remove the plaster cast in case the fracture had not yet healed. She was discharged with the recommendation of analgesic treatment and rest for a week. The girl returned to the emergency room 2 days later demanding to have the cast removed because the pain had become unbearable. When the doctor removed the dressing he observed erythema, edema, and swelling of the hand and right wrist where the bandage (containing Leucoplast, Tensoban, and Tensoplast) was in contact with her skin (Figure, A). The acute phase resolved with topical corticosteroids and oral antihistamines and the patient was referred to the allergy unit.

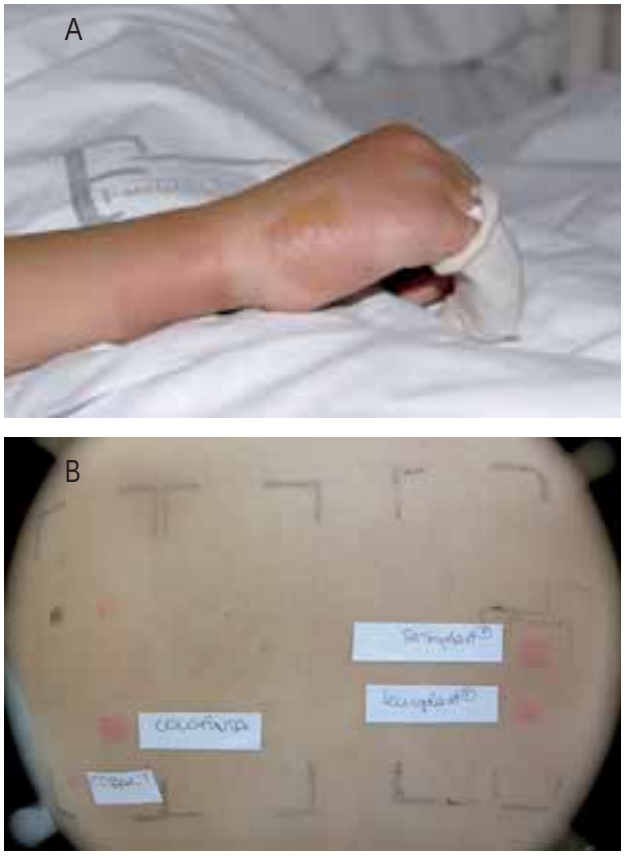

Figure. A, Acute lesion 24 hours after the dressing was removed; B, Patch test at 96 hours after application.

Patch testing was performed 2 months later using the standard series of the GEIDC (Grupo Español Investigación Dermatitis de Contacto [Spanish Contact Dermatitis Research Group]) and the products used for the dressing (Leucoplast, Tensoban, and Tensoplast). Test results were assessed at 48 and 96 hours and were positive for colophony (++), cobalt (+), Leucoplast (++), and Tensoplast (++) (Figure, B).

Our case is interesting for 2 reasons: first the patient was young and contact dermatitis is not common in childhood; and second, although in most medical equipment the replacement of colophony and rubber components (previous related causes) by acrylic polymers has reduced the frequency of contact dermatitis, isolated reactions similar to those experienced by our patient are still described.

Derived from pine trees, colophony is a complex mixture [2]. Unmodified colophony consists of about 90% resin acids. The remaining 10% consists of terpenes, terpene alcohols, sesquiterpene and diterpene hydrocarbons, aldehydes, and alcohols.

Colophony is still widely used, so there are many sources of contact. Unmodified colophony is used in solder fluids, cosmetics (such as depilatory products, soaps, hair spray, hair gel, and nail polish), cutting fluids, insulation material, and adhesives [3]. Hypersensitivity to colophony is more common in professions such as musician, furniture maker, and house painter, because of the direct use of this resin. In a health care setting, colophony allergy may also be observed as a result of reactions to adhesive in skin sutures, adhesive tapes, and sealant in dental prostheses.

There are few studies on the prevalence of allergy to colophony, which stands at between 1% and 3.6%, with the result that the allergen is already part of the standard patch test [4,5].

In summary, we report a case of allergic contact dermatitis due to an uncommon but ubiquitous allergen. Some of the products used in daily clinical practice can cause allergic contact dermatitis and should therefore be borne in mind. Testing for these products is easy, noninvasive, and very informative.

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Antigenic and Allergenic Differences Between Green and Mature Tomatoes

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Key words: Tomato allergy. Ripening. Food allergens. Protein content.

Palabras clave: Alergia a tomate. Maduración. Alérgenos alimentarios. Contenido proteico.

Protein content in fruits increases with ripening and decreases when maturity is reached, thus affecting allergenicity [1,2]. The ripening process is accompanied by quick changes in metabolism and chemical composition, mainly with respect to carbohydrates and proteins [3]. This preliminary study analyzes the immunochemical differences between immature tomatoes and red ripe tomatoes and evaluates their in vitro allergenicity.

Two different tomato peel extracts were prepared following a previously described methodology [4,5]. These were extract A, orchard-cultivated immature green tomatoes that are unsuitable for human consumption, and extract B, ripe Canario tomatoes in optimal conditions for human consumption obtained from a local market. The protein content, measured using the Lowry-Biuret method, was 231.97 µg/mg of freeze-dried material for extract A and 99.30 µg for extract B. The protein profile was analyzed by sodium dodecyl sulfate polyacrylamide gel electrophoresis and silver stained. Specific immunoglobulin (Ig) E to both extracts was measured by direct enzyme-linked immunosorbent assay (ELISA) using a tomato-positive pool of sera (CAP with tomato peel extract = 13.7 kU/L) and the individual sera of 12 Spanish subjects with a positive skin prick test to tomato peel extract (6 male, 6 female; 25 [SD, 7] years old). They were all sensitized to pollens, mainly *Artemisia* and *Salsola*, and 9 were sensitized to other fruits. Six had oral allergy syndrome with tomato, 1 had urticaria with tomato, and 5 were symptom-free with tomato. The allergenic profile was determined by immunoblotting. Inhibition studies were conducted using ELISA and immunoblotting [4].

The protein profile of both extracts showed significant differences (Figure, A). Three tomato allergens—Lyc e 1 (14 kDa), Lyc e 2 (50 kDa), and Lyc e 3 (6 kDa)—and other important proteins of 25 kDa and 31 kDa were observed in both cases but were clearly visible in extract A. Other bands visible in extract A, were not identified in extract B. Different bands with a molecular weight of 9, 15, 31, 46, 50, 60, and 68 kDa showed IgE binding capacity with higher intensity in extract A (Figure, B). Extract A showed higher levels of specific IgE (0.46 OD; range, 0.1-1.41) than extract B (0.34 OD; range, 0.022-1.114) ($P < .01$, paired t test; normality test = 0.189). ELISA inhibition demonstrated that extract A was more potent than extract B (the amount of protein needed to reach the 50% inhibition point was 0.16 µg for extract A and

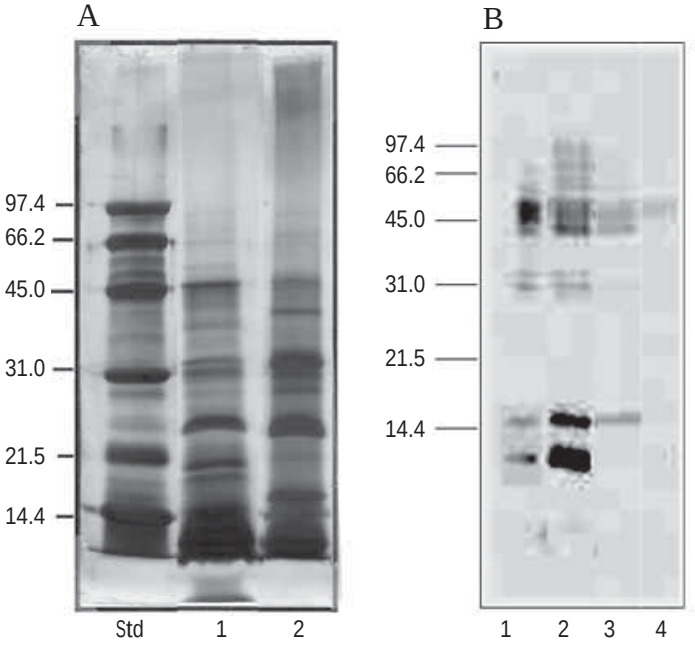

Figure. A, Protein profile of both tomato extracts: Lane 1, green tomato extract; lane 2, mature tomato extract. B, Immunoblot inhibition: Lane 1, extract B (no inhibition); Lane 2, extract A (no inhibition); Lane 3, extract A (inhibition with extract B); Lane 4, extract B (inhibition with extract A).

2.03 µg for extract B). Immunoblotting inhibition experiments demonstrated a higher capacity for inhibition with immature tomatoes. Extract A inhibited nearly all extract B and only soft bands with high molecular weights were visible. Extract A was partially inhibited with extract B. A band of 15 kDa and other bands with high molecular weights were still clearly visible (Figure, B). A band of 46 kDa, which could correspond to polygalacturonase, was more evident in extract B. In fact, the final concentration of polygalacturonase increases significantly during the ripening process (which is regulated by LTPs [5]), and is probably the only allergen whose concentration increases during ripening [6]. Our results are consistent with those of Kondo [7], who has also studied the allergenicity of tomatoes at different maturation points, even if this was not the main focus of the study. Accordingly, in our study, the concentration of the other allergens decreased significantly during maturation.

Although other factors may also affect allergenicity, several studies have found similar results, demonstrating that the maturation process modifies the protein concentration, thus affecting the final protein/allergen composition of the extracts [1-3,8].

Studies with a greater number of variables, as well as further in vivo and in vitro analyses, are needed to elucidate the clinical relevance of these changes and to determine the factors involved in the variability of allergenicity.

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IgE-Mediated Cereal Allergy and Latent Celiac Disease

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Key words: Celiac disease. Cereal Allergy. Corn flakes. Lipid transfer protein (LTP). Alpha-amylase inhibitors.

Palabras clave: Enfermedad celíaca. Alergia a los cereales. Hojuelas de maíz. Proteínas trasportadoras de lípidos. Inhibidores de la alfa amilasa.

Dietary intake of cereals can cause 2 distinct immunologically mediated diseases with gastrointestinal manifestations, celiac disease, and immunoglobulin (Ig) E-mediated food allergy. The pathogenic mechanisms underlying these diseases are different [1] and the coexistence of both diseases seems to be rare [2].

A 4-year-old girl complained of episodes of abdominal pain, gastric fullness, flatulence, and vomiting immediately after intake of foods containing wheat and/or rye. Nevertheless, she did not present any symptoms when she ate oatmeal and a brand of corn flakes made of wheat and corn.

These symptoms started when she was 8 months old. She did not present diarrhea, steatorrhea, weight loss, or failure to thrive. She did not have any relative with a history of celiac disease.

Skin prick tests (mm) were positive for grass pollen (5), palm profilin (5), purified native Tri a 14 (wheat lipid transfer protein) (5), and gliadin (6). They were also positive to wheat (6), barley (4), rye (5), oats (4), rice (5), and corn (4) (ALK-Abelló, Madrid, Spain). A prick-prick test for corn flakes was negative.

Open oral food challenges were negative to corn flakes made of wheat and to soy shake, oatmeal, and rice.

Single-blind placebo-controlled oral food challenge with

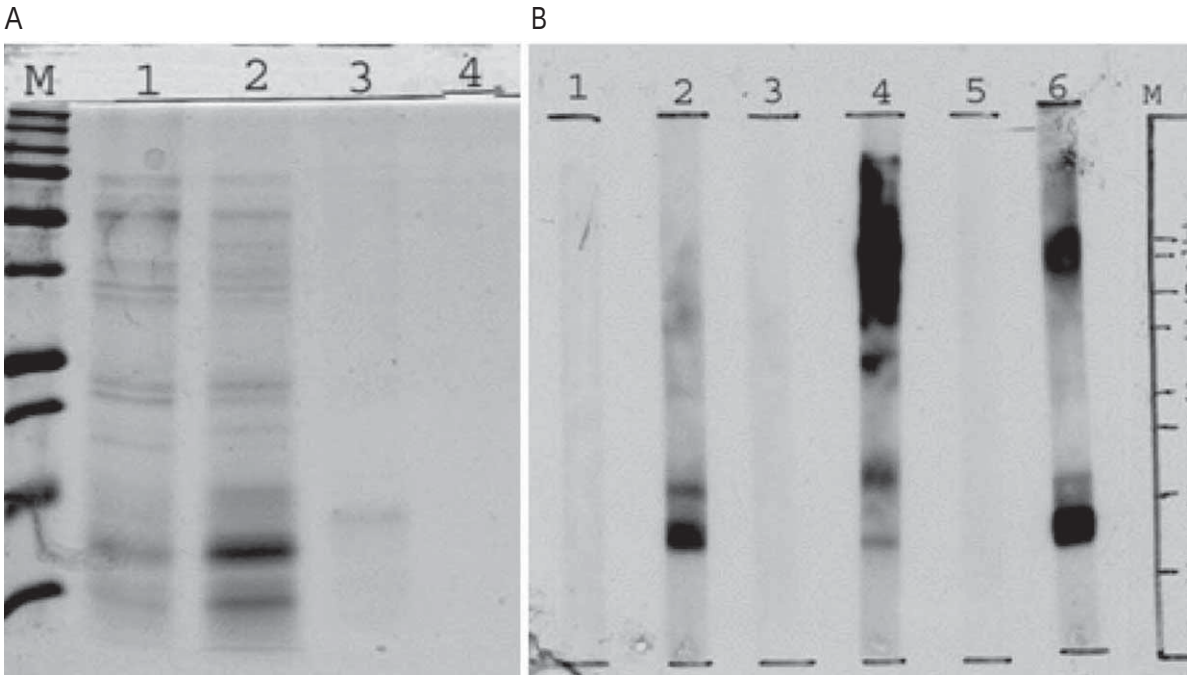

Figure. A. Sodium dodecyl sulphate polyacrylamide gel electrophoresis and Coomassie blue-staining of the oat extract 100 µL (lane 1) and 300 µL (lane 2). Com flakes extract 100 µL (lane 3) and 10 µL (lane 4). Molecular mass markers are indicated (10,15,20,25,37,50,75,100,150, and 250 kDa). B, IgE-immunodetection of the corn flakes extract (lanes 1 and 2), oat extract (lanes 3 and 4), and gliadin extract (lanes 5 and 6). Negative controls with buffer are shown in odd lanes. Molecular mass markers are indicated.

wheat flour mixed with cooked rice induced nausea, abdominal pain, and vomiting 30 minutes after ingestion.

Blood cell count, biochemistry, and Ig determinations were normal. Total serum IgE was 604 IU/mL. Values for specific IgE (Phadia-CAP, Uppsala, Sweden) in kU_A/L were as follows: wheat gluten (14.6), oat (8.37), soy (0.93), rice (0.65), rye (15.3), barley (15.1), malt (24.5), corn (1.8), rBet v 2 (1.7), and Phl p 12 (1.4). Specific IgE (ADVIA-Centaur, Bayer Diagnosis, Germany) to CM3/CM16 (cereal alpha-amylase inhibitors) was 5.30 kU_A/L.

Specific antitissue transglutaminase IgA (anti-tTG) and antigliadin autoantibodies (AGAs) were elevated in the patient's serum (anti-tTG, 629.5; AGAs, 8.1) and in her mother's serum (anti-tTG, 25.5; AGAs, 1.5). The HLA-DQ2 haplotype was detected in both the patient and her mother.

Upper endoscopic examination showed a normal esophagus and stomach, and erythematous duodenal mucosa with slight atrophy. Duodenal biopsies revealed normal mucosa, with slight infiltration of plasma cells and intraepithelial lymphocytes. No eosinophils were observed.

Sodium dodecyl sulphate polyacrylamide gel electrophoresis under nonreducing conditions of the corn flakes and oats extracts are shown in the Figure (A). IgE-immunodetection of corn flakes, oats extract, and gliadin with the patient's serum is shown in the Figure (B). An IgE-binding band of around 14 kDa, which may correspond to the cereal alpha-amylase inhibitors, was detected in all extracts.

An ongoing gluten-free diet was recommended while the patient remained asymptomatic. Six months later, there was a moderate reduction in anti-tTG antibody levels (anti-tTG, 447).

The allergens implicated in this case seem to correspond to amylase/trypsin inhibitor subunits, which were present in all 3-protein fractions of raw and cooked wheat, as well as LTP (Tri a 14). These allergens are the most commonly involved in wheat IgE-mediated food allergy in European patients [3]. In baker's asthma, the amylase/trypsin inhibitor family is also an important allergen together with thioredoxins, peroxidases, prolamins, and LTP (Tri a 14) [4].

Celiac disease is a type of intolerance to the gluten found in several cereals. HLA-DQ2 or HLA-DQ8 is present in 95% of patients. Anti-tTG IgA autoantibodies have 93% sensitivity and 94% specificity in the diagnosis. However, the definitive diagnosis is histologic. The celiac-like intestinal antibody pattern and a high intraepithelial lymphocyte count of the intestinal mucosa may be markers of latent gluten-sensitive enteropathy; some of these patients are clinically gluten-sensitive in the absence of enteropathy [5].

Our patient presented serologic evidence and an HLA haplotype compatible with celiac disease. However, the histological features found did not totally diagnose celiac disease. This could be due to cereal avoidance when the biopsy was performed. Therefore, this presentation could correspond to latent gluten-sensitive enteropathy [5].

In summary, the patient presented an IgE-mediated allergy to cereals and latent celiac disease.

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Addendum

"Coexistence of Asthma and Allergic Rhinitis in Adult Patients Attending Allergy Clinics: ONEAIR Study"
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