

Complement abnormality in Melkersson–Rosenthal

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Key words: cheilitis granulomatosa; C1q; complement; Melkersson–Rosenthal syndrome.

Melkersson–Rosenthal syndrome (MRS) is a disorder of unknown etiology characterized by one or more of the following: episodic lip swelling which progresses to chronicity, facial swelling, intermittent facial nerve palsy, and fissured tongue. Granulomatous infiltration is seen on histopathologic examination of lip tissue (1, 2).

A 13-year-old atopic boy with cheilitis granulomatosa of the lips and complement abnormality.

The first case of MRS with a complement abnormality is reported below.

A 6-year-old Caucasian boy presented with a history of hives as an infant and toddler, and three episodes of urticaria over the preceding 3 years. He was again seen at 13 years of age with the complaint of 6 months of severe lip swelling and additional history of anaphylaxis at 2 and 7 years of age, eczema, and penicillin allergy manifest by angioedema.

On physical examination, there was severe cheilitis with local angioedema, patches of eczema and lop ears having poorly developed antihelical folds. The cranial nerves were intact and the tongue appeared normal.

Pertinent laboratory results were a total eosinophil count of 480 per mm³ (normal < 400 per mm³), immunoglobulin E (IgE) of 597 IU/ml (normal < 200 IU/ml), angiotensin-converting enzyme of 87 U/l (normal 13–100 U/l) and normal chest X-ray.

Positive prick/puncture immediate hypersensitivity skin tests were found to

peanut, tree nuts, mustard, garlic and several seasonal pollens. A RAST test for latex IgE was negative.

Complement evaluation showed a low C1q of 4.6 mg/dl (normal 5.0–8.6 mg/dl) and a C4 at the lowest limit of normal, 16 mg/dl (normal 16–47 mg/dl). Other complement test results were a total complement of 32 U/ml (normal 26–58 U/ml), C2 of 2.7 mg/dl (normal 1.6–3.5 mg/dl), C3 of 129 mg/dl (normal 90–180 mg/dl), chemical test for C1 INH of 16 mg/dl and a functional C1 INH of 87% (normal > 68%).

A lip biopsy showed granulomas with multinucleate giant cells. Stains for fungi and acid-fast bacilli were negative.

This case is compatible with the monosymptomatic form of MRS, which is also termed cheilitis granulomatosa Miescher (3). Other diseases in the differential diagnosis of granulomatous cheilitis seem unlikely in this patient: sarcoidosis because of the normal angiotensin-converting enzyme level and absence of pulmonary, lymphatic, ocular and joint findings and Crohns disease because of the absence of other gastrointestinal signs or symptoms. The patient also has an allergic diathesis.

The complement studies revealed a low C1q and a C4 at the lowest limits of normal. Total complement, C2, C3 and C1 INH were all normal, as has been reported previously in MRS (4). The pathogenesis of the complement abnormality reported here has not been explored, however it could simply be an increased utilization through the classical pathway. If this be the case, then an ongoing immunologic reaction may be a feature of MRS and this would be worth evaluating in additional cases.

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Accepted for publication 28 February 2004

Allergy 2004; 59:362

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Anaphylactic reaction in a patient sensitized to coriander seed

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Key words: anaphylactic reaction; coriander; curry; seed; spice; umbelliferae.

A 42-year-old woman, developed anaphylactic reaction after eating chicken and vegetables in a Birmanian restaurant. When she was studied, she did not know the spices used for preparing the dishes and she has tolerated chicken and vegetables earlier. She had no history of atopy.

Sensitization to coriander seed and other umbelliferae seeds.

Extracts from different spices (coriander seeds, curcuma, fenugreek and two different brands of curry) were extracted in phosphate buffered saline (PBS) at 10% w/v for skin-prick test. They were positive to both curry and coriander seeds. Fruits, vegetables, egg, milk, nuts, fishes and latex were negative. Specific IgE was positive to curry (82.4 kU/l), sesame (4.7 kU/l), and Umbelliferae seeds: coriander (47.8 kU/l), anise (42.1 kU/l) and cumin (17.5 kU/l). It was negative to the Umbelliferae: fresh fennel, dill, parsley and carrot, mustard and others spices (oregano, cardamon, clove and tarragon), birch, mugwort and grass pollen (Pharmacia CAP System, Uppsala, Sweden). The patient did not consent to have a oral challenge test with spices.

Different Umbelliferae seeds (coriander, fennel, anise, cumin, caraway, carrot, celery and parsley), Umbelliferae leaves, seeds of botanically unrelated species (sesame and mustard), curry and a meat seasoning mixture were extracted in PBS (4500 g for 15 min). These extracts were subjected to sodium dodecylsulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and IgE immunoblot (1, 2). In order to purify the strongest IgE-binding protein present in coriander, a 30–60% ethanol gradient fractionation was carried out. This extract was further purified by a reversed-phase HPLC procedure and the high degree of purification obtained allowed the N-terminal amino acid sequence (Centro Nacional de Biotecnología, CSIC).

SDS-PAGE of coriander seeds extract reveals the presence of several high molecular weight proteins, and a broad band close to 11 kDa in the raw extract.

This protein was resistant to the reducing agent 2-ME, but the IgE binding properties of the protein disappeared after treatment with 2-ME (Fig. 1A, B).

Allergens with similar molecular weight can be found in other Umbelliferae seeds (anise, caraway, cumin and parsley), but not in sesame or mustard. The purified 11-kDa protein induced a strong inhibition of the detected seed allergens. The serum detected the presence of allergens in two commercial brands of curry and in a seasoning mixture.

The N-terminal amino acid sequence of the 12 final residues (X-E-S-R-H-S-I-K-N-P-K-Q) showed no homology to other proteins in databases.

Our patient presented an anaphylactic episode shortly after eating food seasoned with unknown spices. The *in vivo* and *in vitro* studies performed detected that the patient was sensitized to an allergen present in Umbelliferae seeds.

The 2S albumins are common allergenic proteins in seeds, identified as major allergens in several edible seeds, such as mustard (Sin a 1), or sesame (Ses i 1) (3). A reducing agent, such as 2-ME, breaks 2S albumins into two smaller subunits (see Fig. 1A, lanes 4 and 5). The molecular weight, the behaviour after treatment with a reducing agent and the N-terminal amino acid sequence demonstrated that this allergen did not belong to the 2S albumin family.

Immediate (type I) and delayed-type (type IV) allergy to these spices are not uncommon (4). Most of the adverse reactions to spices have been reported in mugwort-birch-celery spice-sensitive patients, and homologues to the profilin Bet v2 (14 kDa) are the allergens usually

detected. Proteins similar to the pathogenesis-related protein Bet v1 (17 kDa) and high molecular weight allergens, are often less implicated (4).

The 11 kDa coriander seed protein was also detected in other seeds from the same family. The presence of some of these spices in processed foods, curry or food seasoning mixtures as masked allergens increases the relevance of this allergen. According to these results, the allergen can only be detected when using sample buffer without reducing agents, usually added to the sample to avoid aggregates. This fact can explain why the allergen has not been previously described and we recommend our procedure to patients having positive skin test or specific IgE values to Umbelliferae seeds.

As a conclusion, umbelliferae seeds contain an allergen different from the well-known 2S albumins which is widely expressed in the different seeds of the same family and is present in commercially available seasoning mixtures and curry.

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Accepted for publication 28 February 2003
Allergy 2004; 59:362–363
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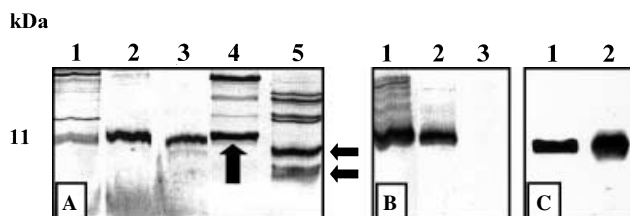


Figure 1. (A): SDS-PAGE (20% acrylamide) of coriander seeds extract. Lane 1: raw extract. Lane 2: result of the ethanol fractionation and 5× concentration of the coriander seeds extract using sample buffer without 2-ME. Lane 3: same as lane 2, but using sample buffer containing 2-ME. Lane 4: mustard seeds extract, sample buffer without 2-ME. Lane 5: same as lane 4 using sample buffer containing 2-ME (arrows mark the heavy and light chain of Sin a 1). (B): Specific IgE detection: antigen extracts and sample buffer as in 1A. (C): HPLC purification of the 11 kDa protein: lane 1, SDS-PAGE, lane 2, IgE immunoblot.

Grape allergy in paediatric population

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Key words: food allergy; fruit allergy; grape; IgE; prick-prick.

We studied 14 children who had suffered allergic reactions involving fresh grapes or grape juice (Table 1). Skin prick test (SPT) with commercial grape extract and with prick-prick technique were negative in five pollinic control subjects without grape allergy history. After parent consent, open oral challenge was performed in two children with 'Muscat de Hamburg' grapes. The rest of parents refused to undergo that possibility.

Using an immunoblotting technique, we investigated sera from five children. An IgE-binding 94 kDa grape protein was recognized by patient no. 8 sera. Patient no. 9 IgE bind to 100, 60, 34, 28, 24 and 17 kDa protein bands, no. 12 to 31 and 24 kDa, no. 13 to a 34 kDa, and no. 14 to a 17 kDa band exclusively.

Grape has only been implicated recently as causative agent of food allergy (1–4).

Double-blind placebo-controlled food challenge is the gold standard for food allergy diagnosis but it requires to spend a lot of time from physicians and family and has the risk of a severe anaphylactic reaction. It would be useful to get a good accuracy in diagnosis using easy and low risk techniques such as SPT, prick-prick or specific IgE, but their sensitivity and specificity are still unknown.

Our results suggest that prick-prick technique with pulp and/or peel from

The aim of this study was to describe a paediatric population with allergic symptoms to grape and to provide some approach to grape allergy diagnosis.

Table 1. Clinical and immunological results of study subjects

Subject no.	Age (years)	Sex	Food*	Onset (min)	Symptoms	SPT† (mm)	H (mm)	Pulp‡ (mm)	Peel§ (mm)	s-IgE¶ (kU/l)	OOC
1	6	F	J	30	U-A	0	5.5	4	3.5	0.78	ND
2	6	M	F	60	Anaph	3.5	9	6	5	0.95	POS
3	6	M	F	10	OAS	ND	6	7	6	0.97	ND
4	14	F	F	5	OAS	4	5	4	3.5	5.08	ND
5	16	F	F	60	Anaph	ND	7	8	8	<0.35	ND
6	4	M	F	60	Anaph	0	6	5	3.5	1.66	ND
7	10	M	F	10	AE	8	6	4	3.5	0.79	ND
8	5	F	F	20	AE	4.5	7	8.5	6.5	1.1	POS
9	10	M	F	30	OAS	4	5.5	4.5	3.5	0.63	ND
10	8	F	J	10	OAS	ND	7	6	4	<0.35	ND
11	14	F	F	5	Anaph	6	9	6.5	5.5	<0.35	ND
12	6	M	F	5	OAS	0	6	3.5	7	4.91	ND
13	16	F	F	5	OAS	3	6.5	6	5.5	2.38	ND
14	7	M	F	240	U	ND	5	6.5	6.5	2.11	ND

H, histamine; U-A, urticaria-angioedema; Anaph, anaphylaxis; OAS, oral allergy syndrome; AE, angioedema; U, urticaria; OOC, open oral challenge; ND, not done.

* Source of triggering food: J, grape juice; F, fresh grape.

† Mean diameter of SPT with grape commercial extract (CBF Leti, Madrid, Spain).

‡ Mean diameter of prick-prick technique with grape pulp (Muscat de Hamburg).

§ Mean diameter of prick-prick technique with grape peel (Muscat de Hamburg).

¶ Serum-specific IgE to grape extract from 'Muscat de Hamburg' by CAP-FEIA in kU/l (Pharmacia-Upjohn, Uppsala, Sweden).

fresh grape could have better results than SPT with commercial extract (4). In the other hand, high allergen-specific IgE concentrations in food allergy, have been taken as predictive of clinical reactivity with certain allergens as egg, milk, peanut and fish (5). However, low specific IgE grape levels shown here indicate that the cut-off could be, as in other fruits and vegetables, lower than with those mentioned food allergens, and it does not appear to have better predictive value of clinical reactivity than SPT. It might cause that standard immunoassays show negative results as suggested by other authors in grape allergy (2, 4).

Immunoblotting reveals that many different allergens are involved in grape allergy. More studies shall be performed to determine both predictive value of all these techniques and the major grape allergens.

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Accepted for publication 13 May 2003

Allergy 2004; 59:364

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Hypersensitivity to maize pollen

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Key words: allergy; asthma; cross-reactions; immunotherapy; Poaceae; pollens; rhinoconjunctivitis; *Zea mays*.

The maize (*Zea mays*) belongs to the family Poaceae. Although maize pollen (MP) is abundantly produced, it is found in low concentrations as an airborne pollen because of its weight. In fact, most MP will fall within 50–70 m from the source. So, it has been widely assumed to be a minor agent of pollinosis.

We report the case of a 55-year-old man with a 16-year history of recurrent episodes of rhinoconjunctivitis and asthma from July to September. Symptoms resolved partly with antihistamines, bronchodilators and corticosteroids. He works in a rural area where maize, fruit trees and vegetables are found in abundance.

Prick tests were performed with a battery including pollens of grasses (*Secale*, *Lolium*, *Cynodon*, *Phragmites*, *Zea mays*), trees (*Olea*, *Quercus*, *Platanus*, *Cupressus*, *Prunus*, *Eucalyptus*, *Morus*, *Robinia*), weeds (*Chenopodium*, *Plantago*, *Parietaria*, *Rumex*, *Mercurialis*), and Compositae (*Artemisa*, *Helianthus*), house-dust and storage mites, molds, animal danders (dog, cat, feathers), cockroach, latex and *Tetranichus urticae* extracts. All of them were negative excepting for MP (10×10 mm).

Total immunoglobulin (IgE) was 1751 IU/ml. Specific IgE (CAP System) to MP was 4.28 kU/l, but negative to grass pollens. Complete blood count, biochemistry, sinus and chest X-rays, and basal spirometry were normal.

A symptom diary was completed by the patient daily during the symptom period for 2 years. We confirmed the severity of

symptoms every year and its relationship with the occupational exposition of the patient to maize cultures. Physical examination at this moment showed conjunctival hyperemia, nasal obstruction, aqueous rhinorrhea, and wheezing.

In view of these results, the patient began immunotherapy with an extract of MP made by ALK-Abelló Laboratory (Madrid, Spain). He received increasing doses during the initiation of treatment and then was followed with a maintenance dose of 0.8 ml monthly (5000 PNU/ml). The assessment of the effect of the immunotherapy was on the clinical symptoms and drug therapy requirements. The patient had a marked improvement. Side effects were negligible.

Our patient had a documented clinical history of seasonal allergic rhinoconjunctivitis and asthma in summer. The climatic characteristics of our area do not favor the cultivation of most of plants during this period, excepting of maize cultures. Interestingly, the time of symptoms of our patient coincided with the maize pollination.

Crossreactivity between grass and MP extracts has been studied by different authors using the RAST inhibition test. Most of them showed a low degree of reactivity (1–3). In addition, others reported that many patients with pollinosis showed positive skin prick tests to MP and not to grasses, while others had positive tests to grass pollens but not to MP (4).

Only one study reported immunotherapy with grass and MP via sublingual (but none with MP alone) with satisfactory results (4).

In conclusion, the MP may be an important allergen in areas dedicated to maize growing, and should be included in panels of allergenic pollens because of little crossreactivity between maize and grass pollens. The immunotherapy with an MP extract is safe and effective.

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Accepted for publication 1 September 2003
Allergy 2004; 59:365

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No decrease of birch pollen specific IgA and IgG in nasal fluids from cortisone treated patients with intermittent allergic rhinitis

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The efficacy of local treatment with glucocorticoids (GC) in intermittent allergic rhinitis (IAR) is well established (1). However, the effects of GC on Bet v 1-reactive immunoglobulin A (IgA) and IgG in birch pollen-induced allergic rhinitis have not been defined. In ragweed-induced

The effects of GC on Bet v 1-reactive IgA and IgG in birch pollen-induced allergic rhinitis have not been defined.

IAR, no change in allergen reactive IgA was found in nasal fluids from patients who received treatment with a topical GC (2). Similarly, GCs induced no change of peripheral IgG levels in healthy volunteers (3). The roles of IgA and IgG in

allergic disease are complex. Allergen-reactive IgA and IgG may offer protection, either by preventing allergen penetration in the mucosa or by inhibiting IgE binding to allergens of identical specificity (reviewed in 4). On the contrary, experimental studies indicate that IgA and IgG may induce degranulation of eosinophils and neutrophils. Allergen-specific IgA and IgG have been demonstrated in nasal secretions from patients with allergic rhinitis sensitive to birch, grass and ragweed, but not in healthy controls. Moreover IgA was positively correlated to nasal fluid eosinophil cationic protein (ECP) and eosinophil derived neurotoxin (EDN) concentrations. Interestingly, no increase of Bet v 1-reactive IgA and IgG were found in patients during season compared with out of season, despite development of symptoms and signs of inflammation, i.e. increased nasal fluid albumin, IgG, eosinophils and ECP (5). This suggested that allergen-specific IgA and IgG might be constitutively released irrespective of the degree of allergic inflammation. If so, how would GCs, which are highly effective inhibitors of allergic inflammation, affect these antibodies? The aim of this study was to examine if treatment with topical GCs would alter nasal fluid concentrations of Bet v 1-reactive IgA and IgG in birch pollen-induced IAR.

Twenty-one patients with birch pollen-induced intermittent allergic were seen after start of symptoms during the birch pollen season, and then given treatment with Fluticasone nasal spray 100 µg in each nostril once daily and Loratadine tablets 10 mg once daily. The patients were asked to return after 2 weeks of treatment. Nasal fluids Bet v 1-reactive and total IgA and IgG were analysed with

enzyme-linked immunosorbent assays as previously described (5). ECP and albumin were determined by competitive radioimmunoassays according to the instructions from the manufacturer (5).

Nasal symptom scores decreased from median (range) 3 (1–9) in patients before treatment with topical GCs to 0 (0–4) after treatment ($P < 0.0001$). Total nasal fluid IgA levels before treatment did not differ, 54.5 µg/ml before compared with 40.3 µg/ml after treatment; IgG, 35.5 µg/ml compared with 6.7 µg/ml ($P < 0.001$). IgA and IgG antibodies reacting with rBet v1 were present in nasal fluid from almost all patients both before and after treatment, but did not differ significantly: Bet v 1 IgA, 8.0 ng/ml before compared with 9.4 ng/ml after treatment; Bet v 1 IgG, 15.8 ng/ml compared with 11.7 ng/ml (Table 1).

By contrast, nasal fluid albumin and ECP decreased after, as compared with before treatment [albumin: 99.5 mg/l (10.4–763) compared with 39.2 mg/l (4.1–338), $P < 0.01$; ECP: 28.1 µg/l (2.6–675) compared with 9.7 µg/l (0.2–139), $P < 0.00001$].

In this study local treatment with GC did not affect nasal fluid total or Bet v 1-reactive IgA. To our knowledge, there is no data on the effects of GCs on total IgA production. In a previous study of ragweed-induced IAR, no difference in local allergen-reactive IgA was found in GC-treated compared with untreated patients (2). IgA is mainly locally produced (6). Taken together, this indicates that GCs do not decrease either total or allergen-reactive IgA production in the nasal mucosa of patients with IAR. By contrast, total IgG decreased following GC treatment. The effect of GC on nasal fluid IgG has not been previously des-

cribed. IgG is a known marker for plasma transudation. By contrast, there are data showing that allergen-reactive IgG antibodies in nasal secretions are mainly locally produced (6). Therefore, decreased IgG could result from decreased plasma transudation, rather than GCs inhibiting local production. This is supported by a concurrent decrease of nasal fluid albumin, and no change of Bet v 1-reactive IgG.

The results of this study should be interpreted with some caution as immunoglobulin concentrations could be confounded by variable dilution of nasal lavage fluids. Moreover, the study was not placebo controlled. However, the observed decreases of ECP and albumin support the validity of our findings.

Taken together, the results of this study indicate that treatment with topical GC does not decrease Bet v 1-reactive IgA and IgG. As these immunoglobulins are found in nasal fluids from most patients with IAR, but not in healthy controls, further studies are warranted to elucidate their function.

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Accepted for publication 10 September 2003
Allergy 2004; 59:365–367
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Table 1. Nasal fluid concentrations of total and allergen-reactive IgA and IgG

	Total IgA (µg/ml)	Bet v 1 IgA (ng/ml)	Total IgG (µg/ml)	Bet v 1 IgG (ng/ml)
Before treatment				
Median	54.5	8.0	35.5	15.8
Range	18.1–199.6	0.7–45.4	2.3–100.3	1.1–167
Number	21	21	21	21
After treatment with a topical glucocorticoid				
Median	40.3	9.4	6.7*	11.7
Range	3.4–137.3	0.6–125.6	0.4–55.8	0–245.9
Number	21	21	21	21

* $P < 0.001$ compared with patients before treatment (Wilcoxon signed rank test).

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Pancolitis after influenza vaccination

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Key words: delayed hypersensitivity; influenza vaccination; pancolitis.

A 70-year-old woman with a history of diabetes mellitus presented with malaise, loss of consciousness, vomiting and bloody diarrhoea 2 h after influenza vaccination (Vaxi-grip®, Aventis Pasteur, Lyon, France). She had already been given influenza virus vaccine six times before. The patient had no history of any adverse drug reaction. Medication at the time of admission was insulin.

Examination revealed pain but not peritoneal signs, blood pressure was 140/80, heart rate 70 beats/min. The remainder of the physical examination was normal. Over the next several days she developed arthralgia of the knees. The spontaneous resolution in 10 days without recurrence was noted. Laboratory studies disclosed the following values: erythrocyte sedimentation rate 18 mm/h,

A case of delayed hypersensitivity induced by influenza vaccination.

haemoglobin 12.5 g/l, leucocyte $7.9 \times 10^9/l$, platelets $258 \times 10^9/l$. An abdominal computed tomographic (CT) scan demonstrated a pancolitis. The patient denied an endoscopy.

A year later the patient was healthy without any digestive symptom. A diagnosis procedure with influenza vaccine was performed. Epicutaneous tests were negative to preservatives of influenza vaccine (thiomersal, formaldehyde) as well as to neomycin. Intradermal tests (IDT) were performed with sequential dilutions (10^{-3} , 10^{-2} , 10^{-1}) and pure influenza vaccine. The IDT were read at 20 min and at 48 h. The 10^{-1} dilution and pure influenza vaccine were positive after 20 min (weal of 7 mm); the delayed reading was positive for 10^{-3} dilution (7 mm), 10^{-2} dilution (7 mm), 10^{-1} dilution (12 mm) and pure (35 mm). A skin biopsy of a positive IDT was carried out and a perivascular moderate mononuclear cell infiltrate was shown, compatible with a delayed reaction: predominance of CD4+ T cells (70%) and some CD8+ cells (30%). Five per cent of these T cells were CD45Ra+, activated cells. Biological tests, including CF basophil activation test and CF lymphocyte activation test were negative to influenza vaccine.

In summary given the skin tests, a delayed type hypersensitivity could be implicated in the pancolitis that occurred within 2 h after the injection and had subsided within 2 weeks. The CT aspect as well as the bloody diarrhoea favoured the hypothesis of a bleeding mucosa linked to a possible vasculitis.

Seventeen cases of vasculitis after influenza vaccination have been published. Five patients had marked gastrointestinal symptoms: two with bloody diarrhoea, two with abdominal cramps and one with extreme anorexia culminating in death. Arthralgia was present in 10 patients, two had documented synovitis. The average age was 65.5 years, women and men were affected equally and in 12 cases the vasculitis regressed with no further reported sequelae (1–10).

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Accepted for publication 27 August 2003
Allergy 2004; 59:367
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Systemic adverse reaction to diclofenac administered by transdermal iontophoresis

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Key words: cutaneous drug reactions; cyclooxygenase inhibitors; nimesulide; NSAIDs; rofecoxib.

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are potent cyclooxygenase inhibitors and among

Systemic reactions to transdermal iontophoresis with NSAIDs might not be so rare.

the most prescribed medications, all over the world. However, their consumption is burdened with sometimes severe side effects, mainly at the gastro-intestinal and the renal level, and, in susceptible individuals, with induction of allergic-like symptoms, resulting in urticaria, angioedema, rhinosinusitis and asthma (1).

In order to minimize these risks, when appropriate, NSAIDs are given topically (2). Particularly, transdermal iontophoresis has been used as an effective delivery procedure in the treatment of rheumatic and post-traumatic conditions by NSAIDs.

We recently reported on a case of systemic adverse reaction to lysine acetylsalicylate administered by transdermal iontophoresis, *bona fide*, the first account in the medical literature (3). Lately, however, we observed another case in which a general adverse reaction occurred upon iontophoresis administration of diclofenac.

A 76-year-old female retiree was being treated with diclofenac, 75 mg daily, intramuscularly, with relation to persistent and painful inflammation of the right sciatic nerve. Ten days into treatment, she complained generalized pruritus, facial angioedema, oral erosive and bullous lesions and tongue swelling, which went into remission in *c.* 20 days, upon immediate discontinuation of the diclofenac treatment and administration of steroids. Approximately 3 months later, in order to control the pain and functional impairment caused by the persistent sciatic neuritis, she started a course of daily transdermal administrations of diclofenac (75 mg), by anodic iontophoresis. After 11 days of treatment, generalized pruritus and erythematous reactions at the iontophoresis electrode application sites (i.e. the lower lumbar part of the back and the right calf) appeared. Symptoms receded in *c.* 1 week, upon discontinuation of the treatment and steroidal therapy. Finally, 1 month later, *c.* 30 mins after assuming nimesulide (a single 100 mg dose, orally), the patient underwent a severe reaction

characterized by intense, generalized pruritus, followed by high fever, oral mucosal erosions and blisters and erythema at the sites of the previous iontophoresis electrode applications.

Treatment with corticosteroids and antihistamines led to remission in *c.* 20 days.

The patient was symptom-free at examination. As expected, no evidence of specific IgE against airborne allergens could be found, as assessed by radioallergen sorbent test (Pharmacia CAP IgE FEIA). Total immunoglobulin (Ig)E were 180 kU/l (normal values: < 100 kU/l). In order to provide her with appropriate medication for treatment of her chronic arthritis, the patient was subjected to oral challenge with rofecoxib, according to a single-blind schedule. Thus, following placebo, 0.1 mg, 1 mg, 3 mg, 6.2 mg, 12.5 mg of rofecoxib were administered sequentially, with an increase every 30 mins.

The drug was tolerated and has been used for at least a few days during the following 2 months. No adverse reactions or side effects have been reported.

General reactions to NSAIDs administered transdermally (in the absence of delivery enhancement by iontophoresis or phonophoresis) are considered infrequent and, usually, prompt gastrointestinal symptoms (4). A comprehensive 1994 survey detected only five cases, out of 18 348 reports of adverse reactions to NSAIDs, in which a general adverse reaction had been triggered by topical administration of a NSAID (5).

The case reported here, characterized by severe cross reactions to diclofenac and nimesulide, is, to our knowledge, the second account of a general reaction to a NSAID (diclofenac) administered by transdermal iontophoresis and it suggests that these reactions might not be so rare, as one would assume. Finally, it is intriguing that the patient tolerated the selective cyclooxygenase-2 inhibitor rofecoxib, whereas underwent severe reactions when the nonselective cyclooxygenase inhibitor diclofenac and the partially selective cyclooxygenase-2 inhibitor nimesulide were used.

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Accepted for publication 25 February 2003

Allergy 2004; 59:367–368

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Positive patch test to azathioprine in inflammatory bowel disease

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Key words: azathioprine; inflammatory bowel disease; patch test.

Inflammatory bowel disease (IBD) is an idiopathic and chronic intestinal inflammation. Its etiology and pathogenesis have not been

definitively elaborated. The incidence varies within different geographic areas but it is about 8–18 per 100 000.

Patch tests with Azathioprine 1% pet. is a safe and reliable tool in the diagnosis of hypersensitivity reactions to this drug.

Ulcerative colitis (UC) and Crohn's disease (CD) are the two major types of IBD. They both share epidemiologic, immunologic, and clinical features but UC is a mucosal disease that involves all or part of colon and CD is a transmural process that can affect any part of the gastrointestinal tract. The mainstay of therapy is sulfasalazine and the other 5-aminosalicylic acid (5-ASA) agents with glucocorticoids in case of moderate to severe affectation. Azathioprine and cyclosporine are immunomodulated drugs commonly employed in the management of aggressive and/or glucocorticoid-dependent disease (1).

A 27-year-old man was referred to our department due to generalized exanthema and fever. He presented with a history of glucocorticoid-dependent ulcerative colitis and cement contact dermatitis. He had a pruriginous, erythematous, maculopapular exanthema that had appeared 1 month after he had been started on oral therapy with salazopyrine, azathioprine, and cyclosporine. It involved 40% of the body. The eruption was accompanied by fever and but not by any clinical, abnormal laboratory values, or endoscopic signs of ulcerative colitis activation. We stopped the therapy and treatment with antihistamines, and systemic corticosteroids was prescribed, and the lesions disappeared after 10 days. He was patch-tested using European standard battery and salazopyrine (Salazopyrine® 500 mg; Pharmacia, Barcelona, Spain) 1% pet. and 5% pet., azathioprine (Imurel® 50 mg; Medeva Pharma, Madrid, Spain) 1% pet., cyclosporine (Sandimmun® amp 250 mg; Novartis Pharma, Rueil-Malmaison, France) 1% pet. and 5% pet. A patch test was positive at D2 and D4 to cromate, azathioprine 1% and 5%. The other patch tests were negative at D2 and D4. Some control patch tests with the same preparations (azathioprine 1%) proved negative.

Azathioprine is relatively well tolerated, although a case of contact dermatitis from azathioprine tablets with a positive reaction on patch testing has been recently described (azathioprine 0.1%) in a person who had been handling these tablets (2).

In our patient, who had been on oral therapy, the positive patch test suggest a

cell-mediated immune response (type IV) associated with a cutaneous eruption. Some authors have showed a role for patch testing in drug-induced maculopapular rashes (3–4).

This case suggest the importance of patch testing not only because it may constitute a safe test but also because it can be a reliable tool in the diagnosis of this type of reactions. Azathioprine 1% pet. is a safe and useful concentration to demonstrate its allergenic potential.

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Accepted for publication 16 June 2003
Allergy 2004; 59:368–369
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Anaphylaxis due to loperamide

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Key words: anaphylaxis; hypersensitivity; immunoglobulin E; intradermal tests; loperamide; meperidine; opioids; pethidine; prick tests.

Loperamide is a pethidine (meperidine) derivative used in the treatment of diarrhea. It is an opioid agonist of μ receptors which mainly acts peripherally. The drug seems to be generally safe, although some

cases of necrotizing enterocolitis have been reported in infants. Central effects such as nausea, dizziness, dry mouth,

abdominal pain, and lethargy occur in a minority of users. Hypersensitivity reactions have not been reported (1).

We report the case of a 10-year-old boy who had nasal congestion, aqueous rhinorrhea, dyspnea, wheezing, cough, labial cyanosis, generalized eruption of erythematous macules, and edema of the right eyelid 5 min after receiving oral loperamide (2 mg) for an acute gastroenteritis. The condition of the patient improved within 2–3 h of parenteral administration of antihistamines and corticosteroids. He was administered loperamide previously without any ill-effects. He was born premature and also had a previous history of prematurity, thalassemia minor, meningococcal meningitis, and allergic rhinoconjunctivitis and asthma to olive pollen. He had no known allergies to drugs.

We studied the patient 1 year after the reaction. Skin prick tests with loperamide and other pethidine derivatives were negative. Intradermal tests were positive with loperamide (0.02 mg/ml) and negative with other pethidine derivatives (Table 1). The same tests were carried out in seven control patients with negative results. We did not perform challenge testing because of the severity of the reaction and because of the clear temporal relationship between the administration of oral loperamide and the adverse reaction.

The value of skin prick testing in opiate-sensitive individuals is uncertain as opiates cause non-specific wheals by direct degranulation of mast cells. Pethidine is a synthetic opioid and *in vitro* studies have shown it to have less direct mast cell degranulating activity than the naturally occurring opiates and its mode of action would be different (2). We have found no studies with its derivative loperamide.

In our case, the clinical history, the previous administration of loperamide

It is the first case reported of anaphylaxis due to loperamide with positive cutaneous tests.

Table 1. Cutaneous tests with loperamide and other meperidine derivatives

Drug	Prick tests		Intradermal tests	
	Concentration	Results	1 : 1000	1 : 100
Loperamide	2 mg/ml	Negative	Negative	Positive
Pethidine (meperidine)	50 mg/ml	Negative	Negative	Negative
Fentanyl	0.05 mg/ml	Negative	Negative	Negative
Alfentanil	0.5 mg/ml	Negative	Negative	Negative

with no ill-effects and the results of intradermal tests suggest an immunoglobulin E-mediated process (3).

The total incidence of opiate sensitivity is unknown, and the differential incidence of anaphylactoid and anaphylactic reactions to opiates is also not known. Only one possible case of an IgE-mediated reaction to papaveretum (4) and three other possible cases of sensitivity to pethidine, morphine and fentanyl have been described in the literature (5,6).

To our knowledge, this is the first reported case of anaphylaxis induced by loperamide. Cutaneous tests have been

useful in diagnosis. We have not found cross-reactions with other pethidine derivatives.

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Accepted for publication 9 January 2004
Allergy 2004; 59:369–370
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