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Antibiotic-induced NSAID intolerance

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Key words: challenge test; drug association; NSAID intolerance.

● NONSTEROIDAL anti-inflammatory drugs (NSAID) are among the most useful drugs, but are the second most often incriminated in adverse drug reactions after antibiotics (1). NSAID intolerance or idiosyncrasy occurs in 1–5% of the general population.

According to the most accepted hypothesis, NSAID intolerance is based on inhibition of the cyclo-oxygenase-1 metabolic pattern (2). The lack of *in vitro* tests able to demonstrate this intolerance makes the diagnosis depend exclusively on drug challenge. The difficulty of the diagnostic work-up increases when the reaction requires the coexistence of more than one factor. A case of antibiotic-dependent NSAID intolerance is reported.

A 25-year-old woman was referred for allergologic work-up after two adverse reactions to amoxicillin. She had suffered a pruritic papular facial rash 3 days after starting therapy with amoxicillin (500 mg t.i.d.) 3 months previously. The second reaction consisted of generalized urticaria with foot and hand angioedema 10 min after taking 500 mg amoxicillin p.o. on day 3 of treatment. Both treatments had been prescribed, together with metamizol capsules (575 mg) for dental abscesses. Since these two episodes, she had tolerated metamizol intake on several occasions.

An allergologic work-up was performed. Specific IgE (Pharmacia FEIA CAP System, Pharmacia & Upjohn, Uppsala, Sweden) to

penicilloyl G and V, ampicillin, and amoxicillin were negative. Penicillin standard skin tests (prick and intradermal reaction) with penicilloyl-polylysine (PPL), minor determinant mixture (MDM), sodium penicillin G 10 000 IU, amoxicillin 20 mg/ml, and ampicillin 25 mg/ml at 15 min, and 48 and 96 h were negative. Simple blind challenges with penicillin G 1 000 000 IU and amoxicillin 500 mg were negative, and the patient was maintained on amoxicillin 500 mg t.i.d. for the following 3 days with no adverse effects.

One month later, the patient reported a pruritic papular facial rash together with hand and foot angioedema 10 min after intake of 500 mg lincomycin p.o., which she had started 3 days earlier with metamizol capsules for an odontologic process.

The study was resumed by performing a 500-mg lincomycin simple blind oral provocation test and maintaining a 500-mg t.i.d. schedule for 5 days, with good patient tolerance. Skin tests with metamizol (prick with 400 mg/ml and intradermal reactions with 0.4, 4, and 40 mg/ml) were negative, and a simple blind oral 575-mg challenge revealed no adverse reactions. The patient continued with 575 mg t.i.d. for 5 days with good tolerance.

A simple blind challenge test using amoxicillin 500 mg t.i.d. simultaneously with metamizol 575 mg t.i.d. was started. Twenty-four hours later, the patient presented with a pruritic papular facial rash, and the challenge was stopped. A simple blind challenge test with amoxicillin 500 mg t.i.d. together with diclofenac 50 mg b.i.d. was performed a week later with the same reaction. In an attempt to find a therapeutic alternative, an open challenge test combining amoxicillin 500 mg t.i.d. with nimesulide 100 mg t.i.d. for 5 days was performed, with good tolerance. The patient continued to use this drug association with no further adverse reactions.

Coadministration of an antibiotic was needed for a positive challenge.

In the present case, the coadministration of a NSAID with an antibiotic was required for development of the adverse drug reaction, as the patient had tolerated the separate intake of both drugs on several occasions, either spontaneously or in challenge tests without problems, thereby complicating the diagnosis of NSAID intolerance.

The underlying mechanism of this reaction could be interference by the NSAID in the arachidonic acid metabolism (cyclo-oxygenase-1 inhibition) pattern, as the patient tolerated the intake of the implicated antibiotic together with nimesulide, a selective cyclo-oxygenase-2 inhibitor NSAID. The precise role of the antibiotic in the development of the reaction remains unknown.

The need for the association of several factors for development of intolerance or allergy has been previously reported (3–5). In these cases, the culpable associations were drug plus exercise (acetylsalicylic acid or nafylpropionic acid-dependent exercise-induced anaphylaxis) (3), food plus drug and exercise (food-dependent exercise-induced anaphylaxis in which the previous intake of an NSAID further worsened the reaction) (4), and drug plus food (anaphylaxis to walnuts and pine nuts induced by the intake of an angiotensin-converting enzyme inhibitor) (5). Nevertheless, no cases of drug-induced NSAID intolerance have been reported to date.

We believe this case report to be interesting in view of the high prevalence of NSAID intolerance, which may be underdiagnosed if a factor association is not considered.

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Oral hyposensitization with celery juice

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Key words: celery-mugwort-spice syndrome; food allergy; food hyposensitization; mastocytosis.

● IMMEDIATE-type allergy to celery is common and can cause severe anaphylaxis. Cross-reactivity to carrots, spices of the Apiaceae family, and many other foods (“celery-mugwort-spice syndrome”) is common in patients with celery allergy (1). As celery is often cut into very small pieces or removed before serving, hidden allergens, as in soups, salads, or sausages, hamper avoidance.

Successful treatment of recurrent anaphylaxis.

We treated a 49-year-old woman who had suffered from seasonal rhinoconjunctivitis for 25 years. Starting about 20 years before, she had recurrent urticaria, flush, and generalized pruritus a few minutes after eating. She soon realized that celery, carrots, and several spices elicited these reactions. She tried to avoid these food items, but she later developed at least eight severe anaphylactic reactions with loss of consciousness while eating at restaurants. Each time, she later learned that the food had been prepared with celery or spices. Milder reactions developed after meals at home about three times a week. For some years, she had noticed the appearance of “freckles” on her trunk and thighs.

Skin examination revealed typical lesions of urticaria pigmentosa, and the diagnosis was substantiated histologically. An increased number of mast cells was also found in a bone-marrow biopsy. There were no indications of other systemic involvement by mastocytosis.

Skin prick tests yielded immediate-type reactions to several pollens including mugwort, celery, carrot, anise, coriander, hazelnut, peanut, and soybean. Specific IgE antibodies were demonstrable by CAP-FEIA to celery (class 1); to mugwort, carrot, apple, and peanut (class 2); to hazel pollen (class 3); and to birch pollen and hazelnut (class 4). Baseline mast-cell tryptase levels in the serum determined repeatedly by UniCAP tryptase were 15.8–18.1 µg/l (normal <13.5 µg/l).

Oral challenge with 1 g raw celery root induced within 5 min a prominent flush of the patient’s face, neck, and trunk; generalized pruritus; facial edema; swelling of the hands; and shortness of breath. Ingestion of 1 g rosemary caused orbital swelling, conjunctivitis, and generalized pruritus, whereas several other spices (black pepper, red pepper, oregano, and caraway; dose each 2 g) and soybean (100 g) were well tolerated.