Adverse reactions to nonsteroidal anti-inflammatory drugs and hypersensitivity to lipid transfer proteins

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Lipid transfer proteins (LTP) constitute a family of proteins widely distributed through the plant kingdom [1].

Allergenic LTP have been identified in tree pollen and weeds, plant food allergen sources and latex. The primary sensitizer agent and the fruit mostly involved seems to be the peach [2].

Allergy to LTP has been mainly described in Italy, Spain and Greece [3] and only exceptionally in the Central and Northern Europe.

The allergenic potential of LTP is influenced by their localization and stability to proteolytic and thermal denaturation: indeed LTP are stable molecules, predominantly present in the fruit peel; it might explain why some LTP-sensitized individuals easily tolerate fruits without peel [4, 5].

Due to its heat and pepsin-resistance, LTP may determine local symptoms such as the oral allergy syndrome and systemic symptoms up to anaphylaxis after the ingestion of fruits and vegetables [6].

Previous studies documented the connection among hypersensitivity to LTP and reactions to nonsteroidal anti-inflammatory drugs (NSAIDS) [7].

We describe the case of a patient, a 33-year-old woman with generalized urticaria and angioedema thirty minutes after eating a veal steak and lettuce; after lunch she also took an oral film of ketoprofen for headache.

Skin prick tests (SPT) with commercial extracts of many plant foods (garlic, peanut, rice, pear, tomato, walnut, hazelnut, apple, peach, banana, onion, wheat, yeast, corn, barley, potato, celery, soy and spinach) were performed.

The patient had positive SPT to apple, hazelnut, peach, soy and celery and specific IgE positive (> 0.35 U/ml) only to apple (0.83 U/ml), peach (1.70 U/ml) and hazelnut (3.73 U/ml). The patient told us she did not eat currently these foods because previously she presented oral allergy syndrome (which includes itching and swelling of the lips, palate and tongue) after their ingestion.

SPT (Alk-Abello, Milan, Italy) with the commercial extracts of LTP and profilin were performed: only LTP was positive; we also detected specific IgE (UniCAP, Phadia, Uppsala, Sweden) for the recombinant allergen Pru p 3 whose value was 0.44 U/ml.

Moreover SPT and patch test with ketoprofen were negative.

Before the reaction she had already taken ketoprofen without symptoms but she had never associated the intake of this drug with the ingestion of lettuce (which is one of the plant foods-containing LTP). When she came to our attention she had already reintroduced veal steak in her diet without presenting reactions.

On the basis of these results we decided to perform an oral test with ketoprofen oral film 80 mg: we diluted the drug in 10 ml of water and we administered increasing doses of this solution every 30 min (1 ml, 2 ml, 3 ml and 4 ml of the solution).

The patient was monitored during this procedure and for 3 h after the last administration.

No symptoms occurred during the test and the patient tolerated the recruitment of ketoprofen also at home. Then she underwent an oral challenge with lettuce: this test was performed in 2 days in the day hospital regimen by administering increasing doses of lettuce starting from 1 mg of lettuce until reaching the dose of 100 g of this food. Challenge was negative and then the patient tolerated lettuce also at home.

This case report shows an important association between hypersensitivity to LTPs and reactions to NSAIDS as reported in other works [7, 8].

Although the association between hypersensitivity to lipid transfer protein and the onset of reactions after taking NSAIDS is only a recent observation, in these

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months we are evaluating other patients referred to our Allergy Unit with a history similar to that of the patient described in our case report. In particular we point out to the cases of 2 other patients:

– a patient with urticaria-angioedema after the ingestion of lettuce followed by the intake of ketoprofen;
– a patient with urticaria after the ingestion of sunflower seeds followed by the intake of ketoprofen.

Both these patients, at the time of the visit, had taken again (but separately) ketoprofen and the foods involved in the reactions by themselves without presenting symptoms.

On the basis of these observations we think that the association between hypersensitivity to lipid transfer protein and reactions after taking NSAIDS is not casual but it implies a pathogenic mechanism on which we are currently working. In the past Asero [7] showed that LTP allergic patients had a > 4 times more frequent history of NSAIDS hypersensitivity than atopic controls. In agreement with previous studies, we hypothesize that NSAIDS might be co-factors in the clinical expression of food allergy by the dysregulation of the epithelial barrier and the increase of the permeability of the gut mucosa: as a result of that, food allergens more easily interact with the patient's immune system.

It is known that certain augmenting factors (NSAIDS, physical exercise and alcohol) may be clinically relevant for some patients [9, 10]: in the case of a suggestive history but a negative oral challenge, one should consider the possible involvement of augmenting factors, always ask for possible augmentation and other risk factors during the recent past [11].

At the moment, on the basis of previous studies and our experience, we recommend to patients sensitized to LTPs avoiding the ingestion of vegetables containing this panallergen during therapy with NSAIDS.

Further investigations are needed to confirm our hypothesis but we believe that these new aspects of the allergic reactions represent an impressive backdrop on which to act in the near future.

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Eleonora Nucera, Alessia Di Rienzo, Simona Mezzacappa – equally contributed.

Conflict of interest

The authors declare no conflict of interest.

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