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# Possible interaction among hypersensitivity to lipid transfer proteins, chronic urticaria, and hypersensitivity reactions to nonsteroidal anti-inflammatory drugs

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## KEY WORDS

*Food allergy, lipid transfer proteins, chronic urticaria, NSAID hypersensitivity*

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In this issue of *European Annals of Allergy and Clinical Immunology*, Asero (1) has made a novel, important contribution to understanding the connections among hypersensitivity to lipid transfer proteins (LTPs), chronic urticaria (CU), and hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs). He performed a prospective study in order to ascertain a possible association between LTP hypersensitivity and CU. Seventy-five consecutive LTP-allergic subjects were asked in order to establish if they suffered or had suffered from CU and had experienced episodes of acute urticaria/angioedema induced by aspirin or other NSAIDs. Subjects with positive histories underwent the autologous serum skin test (ASST). One hundred atopic subjects not sensitised to LTP and 100 subjects with CU served as controls.

Sixteen (21%) of the 75 patients had histories of current or past CU and 7 (9%) of NSAID-induced urticaria. All 16 patients with a history of CU reported that spontaneous wheals were clearly unrelated to the ingestion of plant-derived foods. The ASST scored positive in 9 (82%) of the 11 patients who agreed to undergo such test. LTP-allergic patients showed a significantly higher prevalence of CU than atopic controls (21% vs 6%;  $p < 0.01$ ), as well as a history of NSAID hypersensitivity that was 4 times more frequent (9% vs 2%). Nevertheless, due to low numbers, this difference did not attain the statistical significance. Interestingly, the gender distribution, prevalence of autoreactivity (as assessed by the ASST), and prevalence of NSAID hypersensitivity of LTP-allergic subjects were similar to those of CU controls.

Overall, Asero's study demonstrates an unidirectional association between LTP hypersensitivity and CU. Considering that none of the 100 randomly selected CU patients presented LTP hypersensitivity, Asero hypothesised that, in LTP-allergic subjects, CU and NSAID intake might act as co-factors in the clinical expression of food hypersensitivity. In effect, CU is characterised by an enhanced gastrointestinal permeability (2) that may facilitate the absorption of food allergens. In addition, according to Asero, mast cells of CU patients undergo continuous stimulation, which makes them much more easily excitable by food allergens, turning into a clinical allergy an otherwise asymptomatic sensitisation to LTP. However, this hypothesis needs to be supported by experimental data. In Asero's study, the

percentage of LTP-allergic subjects with positive histories of CU and/or NSAID hypersensitivity displaying positive responses to the ASST is very high (82%, 9 of 11). However, only 11 of the 20 subjects with positive histories agreed to undergo to the ASST. With regard to NSAID intake, it has been shown that aspirin and other anti-inflammatory drugs can increase intestinal absorption of food allergens and contribute to elicit hypersensitivity reactions to them (3). In these cases, neither NSAID intake nor food ingestion alone elicits reactions.

In any case, the association between allergy to LTP and CU deserves to be investigated in larger studies, especially because of the fact that such association seems to be unidirectional.

On the other hand, the observation that a history of NSAID hypersensitivity was more frequent in LTP-allergic patients than in atopic control subjects could have some impact on the diagnostic approach of hypersensitivity reactions to NSAIDs. Considering that hypersensitivity to LTPs is the most frequent primary food allergy observed in Italian adults (4), the ingestion of food containing LTPs could play an important etiologic role in provoking hypersensitivity reactions to NSAIDs in some subjects with a sensitisation to LTPs. For this reason, the diagnostic workup for patients who experienced urticarial/angioedematous or anaphylactic reactions to NSAIDs

taken after a meal containing LTPs should include allergologic exams (both *in vivo* and *in vitro*) in order to detect a sensitisation to LTPs (or any other food allergen) and, in case of positive results, challenges with the suspected NSAIDs (5). This approach could improve the diagnosis of NSAID hypersensitivity reactions by reducing the number of subjects falsely labelled as sensitive to NSAIDs only on the basis of the history. It can also reduce the risk of such reactions by identifying subjects sensitised to LTPs.

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