R. Asero

Hypersensitivity to lipid transfer protein is frequently associated with chronic urticaria

Ambulatorio di Allergologia, Clinica San Carlo, Paderno Dugnano (MI), Italy - E-mail: r.asero@libero.it

Key words

Food allergy, lipid transfer protein, chronic urticaria, NSAID hypersensitivity

Corresponding author
Dr. Riccardo Asero
Ambulatorio di Allergologia
Clinica San Carlo
Via Ospedale 21
20037 Paderno Dugnano (MI), Italy
Phone +39 02 99038470
Fax +39 02 99038223
E-mail: r.asero@libero.it

Summary

Background: *Sparse clinical observations suggest a possible association between food allergy to lipid transfer protein (LTP) and chronic urticaria (CU).* ***Objective:*** *To investigate the possible association between LTP hypersensitivity and CU.* ***Methods:*** *History of CU, and/or of NSAID hypersensitivity was prospectively assessed in 75 consecutive LTP-allergic subjects (M/F 27/48; age 33.6 years); those with positive histories underwent an autologous serum skin test (ASST). 100 atopic subjects not sensitized to LTP and 100 subjects with chronic urticaria served as controls.* ***Results:*** *16/75 (21%) patients had a history of current or past CU. 7 (9%) had a history of NSAID-induced urticaria, and the ASST scored positive in 9/11 patients (82%). By comparison with atopic controls patients showed a significantly higher prevalence of CU (21% vs 6%; $p < 0.01$), a > 4 times more frequent history of NSAID hypersensitivity (9% vs 2%), and a higher prevalence of females ($p< 0.05$). In contrast, patients and controls with chronic urticaria showed a similar sex distribution, prevalence of positive ASST, and prevalence of NSAID hypersensitivity.* ***Conclusion:*** *An unidirectional association between LTP hypersensitivity and chronic urticaria seems to exist. The reasons for this are unclear although it is possible that CU makes mast cells more easily excitable by food allergens. Further, it has been shown that NSAIDs may up-regulate type 1 allergic responses to foods, possibly increasing permeability of the gut mucosa.*

Introduction

Lipid transfer protein (LTP), a heat- and pepsin-resistant plant pan-allergen is the most frequent cause of primary food allergy in Italy (1) as well as in other Mediterranean countries. Due to its highly conserved structure, cross-reactivity to a number of botanically unrelated plant-derived foods is frequently observed although it is generally accepted that the peach acts as the primary sensitizer to this allergen in most cases. The clinical expression of LTP hypersensitivity shows much variability, including contact urticaria (generally induced by peach) in the absence of symptoms following the ingestion of fruits and vegetables, local symptoms such as the oral allergy syndrome, and systemic symptoms up to anaphylaxis. These symptoms may be present in an isolated form or mix up in several combinations. Further, a proportion of LTP-sensitised subjects are occasionally found during the routine diagnostic workup carried out for suspect respiratory allergy and do not report any food-induced problem. Some years ago, the observation of some consecutive LTP-hypersensitive patients reporting also a history of chronic urticaria

(CU) prompted to carry out a prospective study looking for the possible association between LTP hypersensitivity and CU.

Methods

Consecutive adult patients living in the area of Milan with a history of peach allergy (either contact urticaria, oral allergy syndrome or urticaria/angioedema) and shown to be sensitized to LTP by means of positive skin prick test (SPT) with a commercial peach extract containing 30 μg/ml of LTP, Pru p 3, but lacking both the PR-10 allergen, Pru p 1, and profilin, Pru p 4 (ALK-Abello, Madrid, Spain) (2) seen at the allergy department of the Clinica San Carlo during the last 5 years were studied. Patients were thoroughly interviewed about the presence of current or past CU; a history of continuous or recurrent hives with or without angioedema for a period > 6 weeks (3) during the last 5 years was considered as a positive response. Further, in view of the strict association between CU and urticaria induced by nonsteroidal anti-inflammatory drugs (4,5), patients were investigated for episodes of acute urticaria/angioedema induced by aspirin or other NSAIDs. Those with a positive history were asked to undergo an intradermal test with 0.05 ml of fresh autologous serum (ASST; autologous serum skin test) that was performed after Sabroe et al. (6) at least five days after stopping any anti-histamine therapy. The intradermal injection of saline solution (0.9% weight/volume NaCl) and a SPT with histamine 10 mg/ml were used as negative and positive control, respectively. Readings were taken at 30 min; the appearance of a red wheal with a diameter at least 1.5 mm greater than the control saline solution was considered as a positive response (6). Patients gave an informed consent before the start of the procedure. IgE to whole peach were measured by ImmunoCAP (Phadia, Uppsala, Sweden); values < 0.35 kU/L were considered negative. The study was carried out within the routine activity of this allergy centre, and was approved by the IRB.

Results

Seventy-five patients (M/F 27/48; mean age 33.6 years, range 12-79 years) were finally included. 16/75 (21%) had a history of current or past CU, and 1 further patient had a history of food-dependent, exercise-induced anaphylaxis that was not correlated to specific foods. All patients with a history of CU reported that spontaneous wheals were clearly unrelated to the ingestion of plant-derived foods. Seven patients (3 with and 4 without a history of CU) (9%) had a history of acute urticaria following the ingestion of NSAIDs. Altogether, 20/75 (27%) had a history of CU and/or NSAID hypersensitivity. Eleven patients accepted to undergo the ASST; these included 9/16 patients with a history of CU, 1 patient with NSAID hypersensitivity and the patient with exercise-induced anaphylaxis. The ASST scored positive in 7/9 (78%), 1/1 (100%), and 1/1 (100%), respectively.

As control, the prevalence of both CU and NSAID intolerance was assessed in 100 adult atopic subjects with airborne allergy not sensitised to LTP (M/F 54/46, mean age 30.4 years), and LTP hypersensitivity as well as the prevalence of positive ASST and NSAID hypersensitivity was assessed in 100 randomly selected adult subjects (mean age 45 years; M/F 27/73) who presented at this allergy centre for chronic urticaria. Comparisons are shown in table 1. LTP allergic patients showed a significantly higher prevalence of CU than atopic controls (21% vs 6%; $p < 0.01$; chi square test with Yates' correction), and a > 4 times more frequent history of NSAID hypersensitivity (9% vs 2%) although, due to low numbers, this difference did not reach the statistical significance. Further, LTP allergic patients showed a significantly higher prevalence of female patients than atopic controls ($p< 0.05$, table 1). In contrast, the sex distribution as well as the prevalence of

Table 1 - Prevalence of chronic urticaria and NSAID hypersensitivity in atopic subjects sensitized or not sensitized to lipid transfer protein.

	No.	Age	M/F	Positive ASST	CU	NSAID hypersensitivity
LTP	75	33.6	27/48*	9/11 (82%)	16 (21%)**	4 (9%)
Atopic controls	100	30.4	54/46	ND	6 (6%)	2 (2%)
Urticaria controls	100	45.2	27/73	80 (80%)	-	11 (11%)

**p < 0.05 by comparison with atopic controls; ** p< 0.01 by comparison with atopic controls.*

positive ASST and of NSAID hypersensitivity were similar in LTP-hypersensitive patients and controls with chronic urticaria. No chronic urticaria control (0%) scored positive on SPT with the commercial peach extract.

Peach-specific IgE were measured in 24 LTP-allergic patients, and all scored positive (range 0.41-58.1 kU/L). Median IgE levels did not differ between patients with (n=5) or without (n=19) a history of chronic urticaria (6.37 [range 0.92-58.1] kU/L vs 3.81 [0.41-27.6] kU/L; p = NS, Mann-Whitney U-test).

Discussion

This study showed an unidirectional association between LTP hypersensitivity and chronic urticaria. The interpretation of this finding is not easy, as the two conditions seem to have little in common: one is the most frequent primary food allergy observed in Italian adults (1), while the other one is a non-atopic disease that may affect up to 1% of the general population (7) and has frequently an autoimmune/autoreactive origin (8-10). The fact that none of the 100 randomly selected CU patients did show LTP hypersensitivity suggests that in LTP-allergic subjects CU or NSAID hypersensitivity might play a role as co-factors in the clinical expression of food allergy. CU is characterized by enhanced basal gastrointestinal permeability (11) that may facilitate absorption of food allergens. Further, it is possible that in CU patients mast cells undergo continuous stimulation that makes them much more easily excitable by food allergens. If this were the case, the co-existence of CU might turn into clinical allergy an otherwise silent sensitisation to this food allergen. Regarding NSAIDs, it has been shown that aspirin and other anti-inflammatory drugs may up-regulate type 1 allergic responses to foods, possibly by causing an increased permeability of the gut mucosa (12-15). Surprisingly enough, several clinical features of LTP-allergic subjects were similar to those of chronic urticaria controls: sex distribution, prevalence of autoreactivity (as assessed by the ASST), and prevalence of hypersensitivity to NSAID. The association between food allergy to LTP and chronic urticaria deserves to be investigated in larger studies.

References

1. Asero R, Antonicelli L, Arena A, et al. EpidemAAITO: features of food allergy in Italian adults attending allergy clinics: a multicentre study. Clin Exp Allergy 2009; 39: 547-55.
2. Asero R. Plant food allergies: a suggested approach to allergen-resolved diagnosis in the clinical practice by identifying easily available clinical markers. Int Arch Allergy Immunol 2005; 138: 1-11.
3. Greaves MW. Chronic urticaria. N Engl J Med 1995; 332: 1767-72.
4. Settipane RA, Constantine HP, Settimane GA. Aspirin intolerance and recurrent urticaria in normal adults and children. Allergy 1980; 35: 149-54.
5. Asero R. Intolerance to non-steroidal anti-inflammatory drugs might precede by years the onset of chronic urticaria. Allergy Clin Immunol. 2003; 111: 1095-8
6. Sabroe RA, Grattan CE, Francis DM, Barr RM, Kobza-Black A, Greaves MW. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. Br J Dermatol 1999; 140: 446-52.
7. Powell RJ, Du Toit GL, Siddique N, et al. BSACI guidelines for the management of chronic urticaria and angio-oedema. Clin Exp Allergy 2007; 37: 631-50.
8. Hide M, Francis DM, Grattan CEH, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N Engl J Med 1993; 328: 1599-604.
9. Tong LJ, Balakrishnan G, Kochan JP, Kinet JP, Kaplan AP. Assessment of autoimmunity in patients with chronic urticaria. J Allergy Clin Immunol 1997; 99: 461-5.
10. Asero R, Tedeschi A, Lorini M, Salimbeni R, Zanoletti T, Miadonna A. Chronic urticaria: novel clinical and serological aspects. Clin Exp Allergy 2001; 31: 1105-10.
11. Buhner S, Reese I, Kuehl F, Lochs H, Zuberbier T. Pseudoallergic reactions in chronic urticaria are associated with altered gastroduodenal permeability. Allergy 2004; 59: 1118-23.
12. Morisset M, Moneret Vautrin DA. Food anaphylaxis induced by aspirin. Allerg Immunol (Paris) 2001; 33: 147-9.
13. Harada S, Horikawa T, Ashida M, Kamo T, Nishioka E, Ichihashi M. Aspirin enhances the induction of type 1 allergic symptoms when combined with food and exercise in patients with food-dependent exercise-induced anaphylaxis. Br J Dermatol 2001; 145: 336-9.
14. Matsuo H, Morimoto K, Akaki T, et al. Exercise and aspirin increase levels of circulating gliadin peptides in patients with wheat-dependent exercise-induced anaphylaxis. Clin Exp Allergy 2005; 35: 461-6.
15. Izumi K, Aihara M, Ikezawa Z. Effects of non-steroidal anti-inflammatory drugs (NSAIDs) on immediate-type food allergy. Analysis of Japanese cases from 1998 to 2009 Arerugi 2009; 58: 1629-39.