ORIGINAL ARTICLE

Tomato Allergy: Clinical Features and Usefulness of Current Routinely Available Diagnostic Methods

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Abstract

Background: Tomato contains many allergens but their clinical relevance is poorly defined and the usefulness of available diagnostic methods is unknown.
Objective: To assess the clinical usefulness of current diagnostic methods for tomato allergy.
Methods: Ninety-six adults with plant food allergy were grouped based on their reactivity to PR-10, profilin, and lipid transfer protein (LTP). Tomato allergy was ascertained by history and a positive skin prick test (SPT) to fresh tomato. SPT with a commercial extract and immunoglobulin (Ig) E measurements were carried out.
Results: In total, 36%, 8%, 28%, 18%, 8%, and 1% of patients were sensitized to PR-10, profilin, both PR-10 and profilin, LTP alone, LTP plus PR-10 or profilin, and genuine tomato allergens, respectively. Tomato allergy was detected in 32 (33%) of the 96 patients and was significantly associated with profilin hypersensitivity ($P<.001$). The sensitivity of SPT was good in all subgroups, but specificity was poor in many cases. ImmunoCAP sensitivity was acceptable in profilin reactors, but very poor in PR-10 reactors. IgE levels were not associated with tomato allergy in any of the subgroups. Similarly, birch and peach-specific IgE levels were not associated with tomato allergy in PR-10/profilin or in LTP reactors, respectively. Both SPT and ImmunoCAP worked well in the only patients with true tomato allergy. Birch- and tomato-specific IgE levels were not associated in patients monosensitized to PR-10, but they were correlated in profilin groups ($P<.005$). Peach- and tomato-specific IgE levels were correlated ($P<.001$) in LTP-allergic patients.
Conclusions: Tomato allergy occurs via sensitization towards different proteins. Component-resolved diagnosis helps to define clinical subgroups with different risk levels.

Key words: Tomato. Component-resolved diagnosis. Cross-reactivity. Oral allergy syndrome.

Resumen

Introducción: El tomate contiene numerosos alérgenos cuya relevancia clínica , así como la utilidad de los métodos diagnósticos disponibles, están por definir. Objetivo: Evaluar la utilidad clínica de los métodos de diagnóstico en alergia a tomate.
Métodos: Para ello se estudiaron 96 adultos con alergia alimentaria a vegetales y su reactividad frente a proteínas PR-10, profilina y LTP. La alergia a tomate fue definida por historia clínica y prueba cutánea (prick) positiva a tomate fresco. Se realizaron pruebas cutáneas con extracto comercial de tomate y determinación de IgE específica.
Resultados: Un 36%, 8%, 28%, 18%, 8%, y 1% de los pacientes estaban sensibilizados a PR-10, profilina, ambas (PR-10 y profilina), LTP sola, LTP más PR-10 o profilina, y alérgenos genuinos del tomate respectivamente. 32/96 (33%) de los pacientes tenían alergia a tomate; alergia que se asocia a hipersensibilidad a profilinas ($p< 0,001$). La sensibilidad del prick fue buena en todos los subgrupos, pero la especificidad fue baja. La sensibilidad del ImmunoCAP fue aceptable en los reactores a profilina, pero muy pobre en reactores a PR-10. Los niveles de IgE no se asocian con la alergia al tomate en ningún subgrupo. De forma similar los niveles de IgE específica frente a abedul y melocotón no se asociaban con alergia a tomate en PR-10/profilina, o en reactores a LTP, respectivamente. Ambos test funcionaron bien en los alérgicos genuinos a tomate. Los niveles de IgE específica a tomate y abedul no estaban asociados en los pacientes monosensibles a PR-10, pero se correlacionaban en el grupo de profilinas ($p < 0,005$). Los niveles de IgE específica frente a tomate y abedul se correlacionaban en los pacientes alérgicos a LTP.
Conclusiones: La alergia a tomate ocurre vía sensibilización a diferentes proteínas. El diagnóstico basado en componentes ayuda a definir los subgrupos clínicos con un riesgo diferente.

Palabras clave: Tomate. Diagnóstico basado en componentes. Reactividad cruzada. Síndrome de alergia oral.

Introduction

Tomato (*Lycopersicon esculentum*) is one of the most frequently consumed vegetables worldwide and is also a rather frequent cause of food allergy. Although a number of specific allergen proteins have been identified in tomato, including Lyc e 2 (fructofuranosidase; molecular weight [mw], 50 kDa), Lyc e chitinase (31 kDa), Lyc e glucanase (55 kDa), Lyc e peroxidase (44 kDa), Lyc e 11S (a legumin-like protein), Lyc e vicilin, and others, genuine tomato allergy is extremely rare [1,2]. Most cases of sensitization (positive skin or in vitro tests in the absence of clinical symptoms) and clinical allergy to this food occur in individuals primarily sensitized to other airborne or food allergen sources as a consequence of cross-reactivity. In a recent Italian epidemiological study only 1% of food-allergic patients had tomato allergy but, among those allergic to plant-derived foods, the prevalence was 16% in individuals with pollen-food allergy syndrome and only 0.5% in those with genuine vegetable food allergy [3]. Allergens involved in such cross-reactivity phenomena include Lyc e 1 (profilin; mw, 14 kDa) [4], Lyc e 3 (lipid transfer protein [LTP], 9 kDa) [5,6], and Lyc e 4 (a PR-10 protein homologous to the major birch pollen allergen, Bet v 1; 17 kDa) [7]. Most allergic reactions to tomato are local (ie, limited to the mouth and throat) and are observed in patients sensitized to profilin [8], although a recent report described a severe systemic reaction to tomato in a patient allergic to LTP [9]. Diagnosis of tomato hypersensitivity using in vitro recombinant tomato allergens is currently impossible. This study aimed to assess the clinical performance and usefulness of currently available routine diagnostic methods for tomato allergy in a large group of patients sensitized to different cross-reacting plant panallergens and with different types of plant food allergies.

Methods

Patients

Ninety-six consecutive patients (34 males/62 females; mean age, 38 years; range, 11-78 years) with plant food allergy seen at the allergy department of the Clinica San Carlo in Paderno Dugnano, Italy, during 2011 were studied. Plant food allergy was diagnosed in the presence of a clear-cut clinical history of oral allergy syndrome (OAS) (immediate itching of the lips, tongue and oral mucosa with or without angioedema), gastrointestinal symptoms (gastric pain or cramps, diarrhea, and/or vomiting), urticaria, and/or anaphylaxis following the ingestion of plant-derived foods confirmed by positive skin prick testing (SPT) with fresh material and/or commercial food extracts. Equivocal cases (ie, patients reporting symptoms other than those listed above) were considered to be nonallergic. Tomato allergy was investigated by a thorough interview and confirmed using the same clinical criteria as above (ie, a history of OAS, gastrointestinal symptoms, urticaria, and/or anaphylaxis). Since only patients with a clear-cut history of tomato allergy and a markedly positive SPT were regarded as clinically allergic, confirmative oral challenges with tomato were not carried out.

Patient Classification

Patients were classified into homogeneous groups on the basis of their hypersensitivity patterns. They all underwent SPT with commercial natural date palm pollen profilin purified by affinity chromatography with a poly-L-proline-Sepharose (50 μg profilin/mL; ALK-Abellò) [10] and with a commercial peach extract containing 30 μg/mL of lipid transfer protein (ALK-Abellò). Immunoglobulin (Ig) E to rBet v 1 was also measured by ImmunoCAP (Thermofisher Phadia) in all individuals. In previous studies SPTs to both products have been shown to be highly specific and sensitive for the diagnosis of hypersensitivity to profilin and LTP, respectively [8,11-13]. PR-10 (Bet v 1) IgE reactivity was detected in vitro due to the lack of a reliable in vivo test. (The test used in a previous study [11] was no longer available.)

Based on the results of these in vitro and in vivo tests, patients were classified as shown in Table 1.

Table 1. Classification of Patients Based on in Vivo and in Vitro Diagnostic Test Results

Category	Features
Pure PR-10 reactors	rBet v 1^+/profilin$^-$/LTP$^-$
Pure Profilin reactors	rBet v 1^-/profilin$^+$/LTP$^-$
Both Pr-10 and profilin reactors	rBet v1^+/profilin$^+$/LTP$^-$
Pure LTP reactors	rBet v 1^-/profilin-/LTP$^+$
Blended reactors	positive for LTP plus profilin and/or PR-10
Genuine tomato reactors	rBet v 1^-/profilin$^-$/LTP$^-$

Abbreviation: LTP, lipid transfer protein.

In Vivo and In Vitro Tests

All patients underwent SPTs with commercial extracts of the main pollens present in our area (grass, mugwort, ragweed, plantain, pellitory, birch, cypress, and olive) (Allergopharma) and with a commercial extract of tomato (1/20 W/V, ALK-Abellò). All SPTs were carried out following established methods using disposable skin lancets (ALK-Abellò). Histamine 10 mg/mL and saline were used as positive and negative controls, respectively. Readings were taken at 15 minutes, and wheals with a mean diameter exceeding 3 mm were considered positive.

Tomato-specific IgE was measured by ImmunoCAP in all cases. IgE to whole birch pollen extract and peach extract were also measured in individuals with a positive SPT to birch pollen and peach, respectively. In vitro tests were performed following the manufacturers' indications; IgE levels exceeding 0.35 kU/L were considered positive.

Data Analysis

The accuracy and clinical usefulness of both in vivo and in vitro tests in the different subgroups of patients were assessed using the method of Goldman [14] by calculating:

Prevalence (P): clinical allergy/patients
Sensitivity (SE): TP (true positive)/ TP + FN (false negative)
Specificity (SP): TN (true negative)/TN + FP (false positive)
Positive predictive value (PPV): TP x P/TP x P + FP (1 - P)
Negative predictive value (NPV): TN (1 - P)/TN (1 - P) + FN × P

TP was defined as a positive SPT or IgE measurement in a patient with a clinically confirmed history of allergy, FP as a positive SPT or IgE measurement in a nonallergic patient, TN as a negative SPT or IgE measurement in a nonallergic patient, and FN as a negative SPT or IgE measurement in a patient with a clinically confirmed history of allergy.

Proportions were compared using the χ^2 test with Yates correction and specific IgE levels using the *t* test.

Correlation coefficients (r) after Pearson were calculated between birch pollen-specific IgE and tomato-specific IgE levels in patients sensitized to PR-10 (either with or without cosensitization to profilin). In patients sensitized to LTP the correlation coefficient was calculated between peach IgE and tomato IgE.

Probability values of less than 5% were considered positive. All clinical investigations were carried out according to the principles expressed in the Declaration of Helsinki, and all patients gave their informed consent to diagnostic procedures. Since the study was carried out retrospectively based on data stemming from routine clinical activity, approval by an ethics committee was not needed.

Results

Of the 96 patients studied, 35 (36%) were pure PR-10 reactors, 8 (8%) were pure profilin reactors, 27 (28%) were both PR-10 and profilin reactors, and 17 (18%) were pure LTP reactors. Eight patients (8%) were sensitized to LTP plus profilin (n=7) and/or PR-10 (n= 4), and 1 (1%) had genuine tomato allergy (Table 2).

Altogether, 32 (33%) of the 96 patients (6 males/26 females; mean age, 36 years; range, 11-56 years) had tomato allergy. All but 2 reported typical OAS as the only clinical expression of this allergy. Of the 2 patients without OAS, 1 (notably the only one with genuine tomato allergy) had severe tomato-induced gastrointestinal symptoms, and the other (a pure LTP reactor) had a history of OAS followed by generalized urticaria and hypotension after eating tomatoes. Clinical allergy to tomato was significantly prevalent in female patients ($P<.05$).

Table 2 summarizes the prevalence of tomato allergy in the different subgroups, as well as the results and clinical usefulness of both in vivo and in vitro tests with commercial tomato extracts. Altogether, 78 (81%) of the 96 patients had pollen-food allergy syndrome, defined as plant food sensitization most probably following primary pollen sensitization. Tomato allergy was markedly associated with profilin hypersensitivity, as 23 [55%] of the 42 profilin reactors and only 9 (17%) of the 54 non-profilin reactors reported allergic reactions to tomato (P<.001).

In all subgroups, the sensitivity of tomato SPT ranged from good to excellent; in contrast, due to the high prevalence of false positive results, specificity and PPV were poor in many cases. The NPV of SPT was generally good (Table 2).

Tomato-specific IgE levels ranged between 0 kU/L and 22.10 kU/L. In general, the performance of the in vitro test was poorer than that of the SPT (Table 2). In the pure PR-10 reactor group, the ImmunoCAP was unable to detect any of the 6 tomato-allergic individuals and only produced slightly positive scores (0.36, 0.36, 0.55, and 0.66 KU/L, respectively) in 4

Table 2. Classification of Study Patients, Allergy to Tomato, and Performance of Diagnostic Tests for Tomato in 98 Patients With Plant Food Allergy.

	Pure PR-10	Pure Profilin	PR-10+Profilin	Pure LTP	Mixed Group[a]	Genuine Tomato
	35	8	27	17	8	1
Tomato allergy, No. (%) of patients	6 (17%)	5 (62%)	14 (52%)	2 (12%)	4 (50%)	1 (100%)
Positive SPT to tomato, No. (%) of patients	21 (60%)	7 (88%)	25 (93%)	7 (41%)	8 (100%)	1 (100%)
SE	83%	100%	93%	100%	100%	100%
SP	45%	33%	8%	67%	0%	100%
PPV	6%	80%	54%	5%	50%	–
NPV	98%	100%	48%	100%	–	–
Positive CAP with tomato, No. (%) of patients	4 (11%)	4 (40%)	24 (81%)	7 (41%)	8 (100%)	1 (100%)
SE	0%	40%	93%	50%	100%	100%
SP	86%	33%	31%	60%	0%	100%
PPV	0%	62%	63%	4%	50%	–
NPV	95%	17%	79%	98%	–	–

Abbreviations: LTP, lipid transfer protein; NPV, negative predictive value; PPV, positive predictive value; SE, sensitivity; SP, specificity; SPT, skin prick test.
[a]The mixed group included LTP-hypersensitive patients who were also sensitized to profilin (n=7) and/or PR-10 (n=4).

individuals who tolerated tomato. The NPV of ImmunoCAP was excellent in all PR-10 and LTP reactors, but very poor in pure profilin reactors. A significant association between tomato-specific IgE levels and the occurrence of clinical allergy to tomato was not observed in any of the subgroups. Similarly, birch pollen–specific IgE levels were not associated with tomato allergy in pure PR-10, pure profilin, or PR-10 plus profilin reactors, and peach-specific IgE levels were not associated with tomato allergy in the pure LTP subgroup.

Interestingly, both the in vivo and in vitro tests detected the only genuine tomato-allergic patient in the study group.

No correlation was observed between birch pollen–specific IgE levels and tomato-specific IgE levels in patients monosensitized to PR-10. In contrast, a statistically significant correlation was seen in patients sensitized to both PR-10 and profilin (r= 0.50; $P<.005$) and in those monosensitized to profilin (r=0.86; $P<.005$). Similarly, in LTP-allergic patients, peach-specific IgE levels were significantly correlated with tomato-specific IgE levels (r= 0.73; $P<.001$).

Discussion

Although several allergens have been identified in tomato to date, none are currently available for in vitro component-resolved diagnosis. As a consequence, the diagnosis of tomato allergy is still based on SPTs with fresh food or commercial whole tomato extract and on whole tomato–specific IgE measurements, with the possible adjunct of oral challenges. In a routine setting, component-resolved diagnosis of tomato allergy can currently be inferred only indirectly, using IgE reactivity to specific cross-reacting plant panallergens (ie, profilin, Bet v 1 as a PR-10 representative, and LTP) as surrogate markers of hypersensitivity to different tomato allergen proteins. Of course, such an approach does not work if patients are sensitized to both cross-reacting panallergens and tomato-specific proteins. However, in view of the extreme rarity of genuine tomato allergy [3], there are probably very few patients with such a profile.

The present study analyzed retrospectively the clinical usefulness of the 2 most common routine diagnostic tests for tomato allergy, namely a commercial SPT and ImmunoCAP, in 98 patients with plant food allergy, several of whom were allergic to tomato. The prevalence of the different subsets of plant food allergies seen in this study is consistent with figures reported by a recent multicenter Italian survey [3]. Furthermore, although tomato-allergic patients were detected in all subgroups, in keeping with previous studies, tomato allergy was clearly associated with profilin hypersensitivity [8,15]. In patients monosensitized to lipid transfer protein or PR-10, tomato allergy occurred in a minority of cases (about 15%). The association between tomato allergy and profilin sensitization is probably the result of the high homology between Lyc e 4 (the tomato profilin) and other profilins; for instance, its homology with Bet v 2 (the birch profilin) is about 75% when the sequences of the 2 allergens are compared using NCBI's BLAST software (http://blast.ncbi.nlm.nih.gov/Blast.cgi). In contrast, using the same software, the identity of Lyc e 4 and Bet v 1 (the PR-10 proteins from tomato and birch) and of Lyc e 3 and Pru p 3 (LTPs) is about 42% and 49%, respectively.

SPT with commercial tomato showed satisfactory sensitivity in all subgroups of patients. In this respect it performed better than ImmunoCAP, particularly in individuals sensitized to PR-10. The absence of any correlation between birch pollen–specific IgE and tomato-specific IgE levels in pure PR-10 reactors, along with the very low levels of tomato IgE detected uniquely in some tomato-tolerant individuals suggests that Lyc e 4, the tomato PR-10, either shows limited cross-reactivity with Bet v 1 or is virtually absent in the ImmunoCAP extract. Although the amino acid identity between Bet v 1 and Lyc e 4 is only about 40%, suggesting limited cross-reactivity between the 2 homologous allergens, the results of tomato SPT suggest that the second hypothesis (lack of Lyc e 4 in ImmunoCAP) is probably the right one.

The sensitivity of ImmunoCAP was less brilliant that that of tomato SPT, also in pure profilin reactors. The strong correlation between birch pollen–specific IgE and tomato-specific IgE levels found in profilin reactors suggests that such a defect in sensitivity is probably due to the low levels of profilin-specific IgE in the sera from some tomato-allergic patients.

The specificity of both in vivo and in vitro tests was poor in many cases due to the presence of several false-positive patients, a problem that has also been observed in recent studies of plant food allergy using recombinant allergens [16], as well as in older studies [17]. The same problem makes it difficult to use fresh material for SPT. Why certain patients are able to perfectly tolerate foods to which they are sensitized remains unclear.

Previous studies have shown a correlation between birch pollen–specific IgE levels and the prevalence of clinical allergy to foods containing allergens homologous to Bet v 1, the major birch pollen allergen [18,19]. Such a correlation was not found here, confirming that Lyc e 4 is less homologous to Bet v 1 than other food PR-10 proteins, such as Mal d 1 from apple or Dau c 1 from carrot (see above).

The significant correlation between birch pollen–specific IgE and tomato-specific IgE in the subgroups of patients sensitized to profilin suggests the presence of Lyc e 1, the tomato profilin, in ImmunoCAP. Similarly, the correlation between peach-specific IgE levels and tomato-specific IgE levels in LTP-hypersensitive patients suggests the presence of Lyc e 3, the tomato LTP, in ImmunoCAP although, probably due to the limited homology between Pru p 3 and Lyc e 3 (see above), only a minority of LTP-hypersensitive patients develop clinical allergy to tomato and score positively in in vivo and in vitro tests.

The only genuine tomato-allergic patient reacted to a 9-kDa heat-labile, pepsin-resistant protein [1] that is clearly present in both commercial SPT and ImmunoCAP. It cannot be ruled out that this patient was monosensitized to tomato LTP in the absence of reactivity to peach LTP, but this seems unlikely as the offending allergen was heat-sensitive [1]. Nonetheless, since this allergen was not sequenced, its nature remains undetermined.

The fact that reactivity to other unique tomato allergens (Lyc e 2, Lyc e chitinase, Lyc e glucanase, Lyc e peroxidase, Lyc e 11S, Lyc e vicilin, and others) was not detected in the

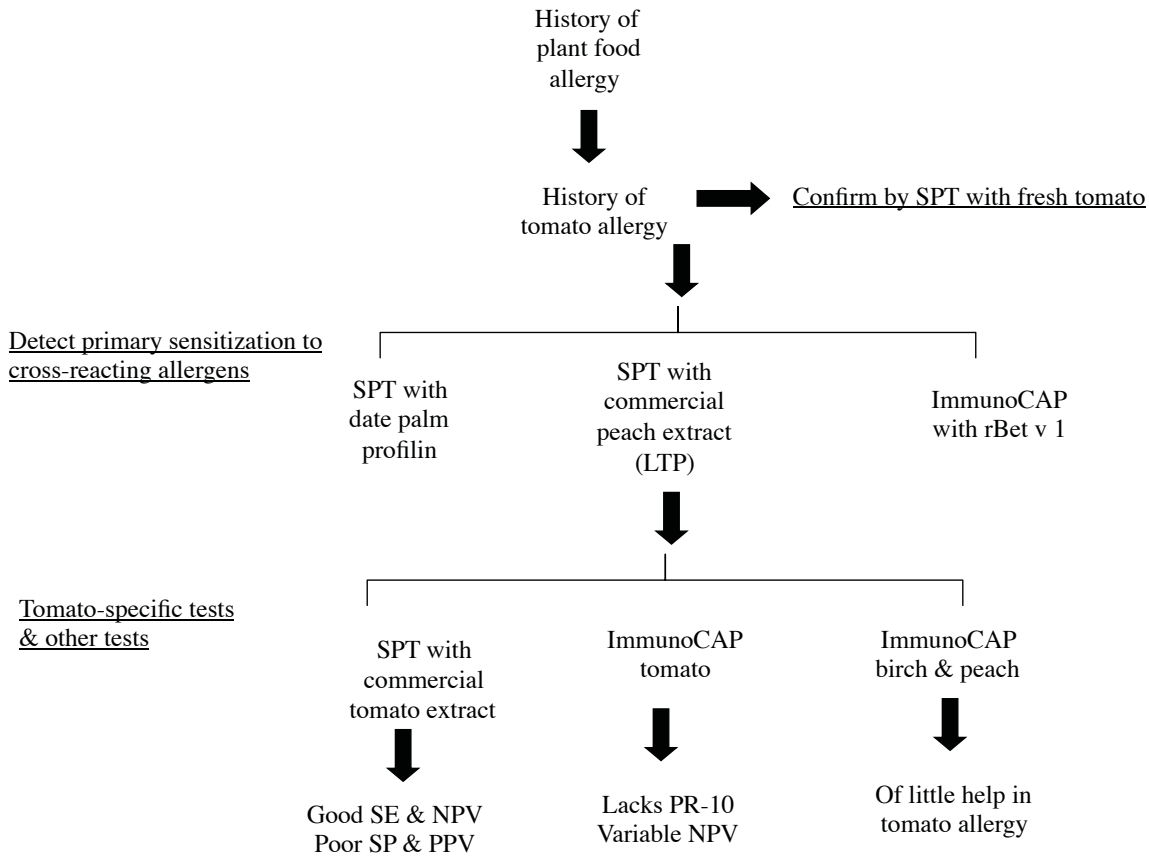

Figure. Proposed diagnostic algorithm for patients with tomato allergy based on currently available tests. Abbreviations: LTP, lipid transfer protein; NPV, negative predictive value; PPV, positive predictive value; r, recombinant; SE, sensitivity; SP, specificity; SPT, skin prick test.

only genuine tomato-allergic patient raises doubts regarding the true clinical relevance of these allergens.

In conclusion, tomato allergy occurs via sensitization towards different proteins. Although differences between tomato cultivars may exist [20], most cases are observed in profilin-hypersensitive subjects and are mild. Component-resolved diagnosis helps the clinician to define clinical subgroups with different risks. A summary of the diagnostic algorithm employed in this study is shown in the Figure.

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