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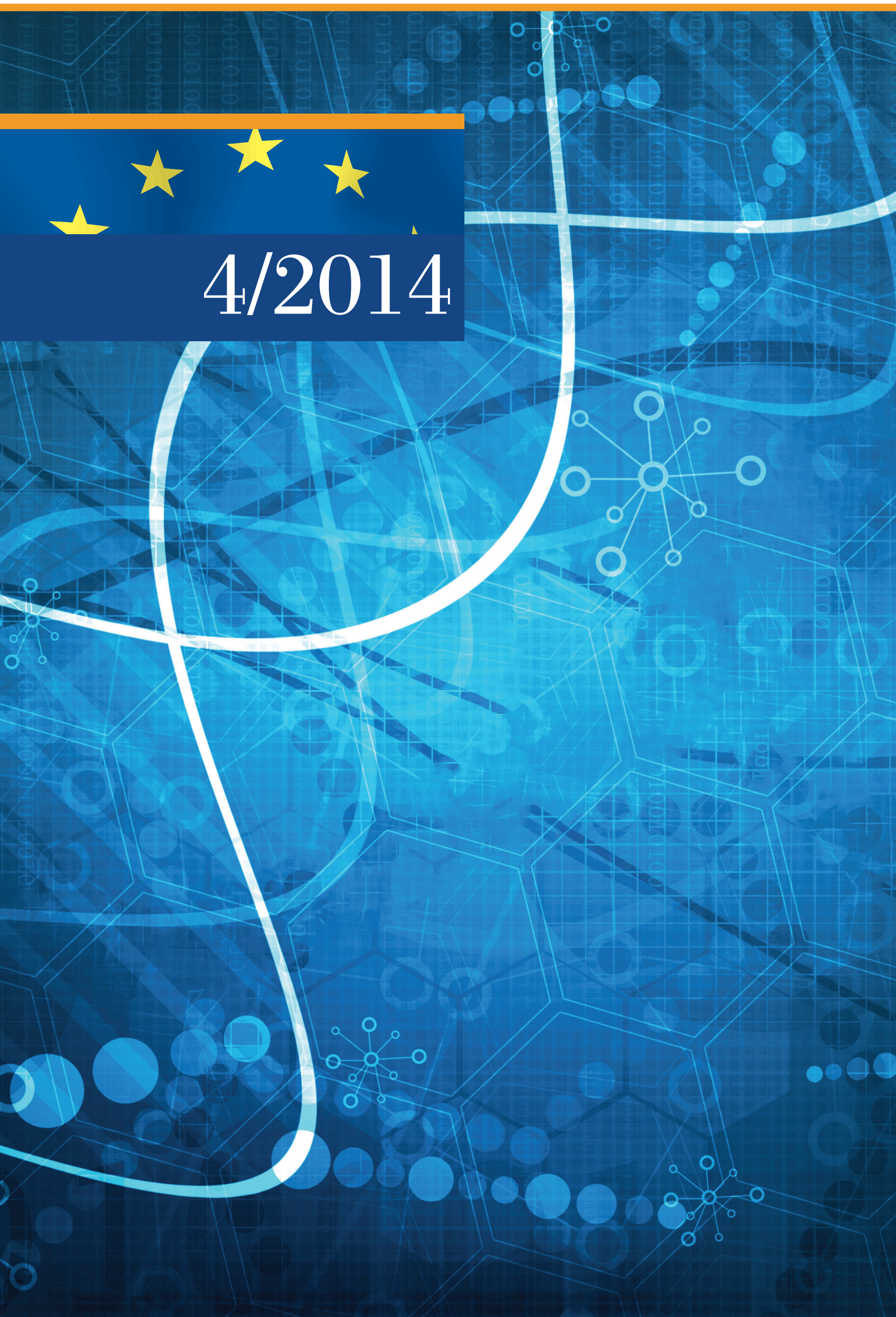

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Original Articles

Case Reports

C. Lombardi[1], G.W. Canonica[2], G. Passalacqua[2]

The perception of allergen-specific immunotherapy among chest physicians: an Italian survey

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Key words

Allergen-specific immunotherapy; chest physicians; asthma; allergic rhinitis

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Summary

Background and Aim. *This questionnaire-based study evaluated the overall level of knowledge about allergen-specific immunotherapy (SIT) among chest physicians, who are frequently involved in the management of respiratory allergies. This represents an interesting aspect, because chest physicians intercept many of the patients with allergic rhinitis w/wo asthma, in which SIT could be potentially indicated.* ***Methods.*** *A panel of experts prepared a questionnaire, involving 16 main points of interest/questions concerning the knowledge and use of SIT. Questionnaires were e-mailed (September-October, 2011) to randomly-selected specialists, and were returned anonymously.* ***Results.*** *81 questionnaires from specialists using SIT were eligible. The respondent population had a mean age of 51 years (range 33-63 years, 74% male). The general knowledge on SIT is overall satisfactory among pulmonologists, and they are well aware that SIT is recommended in the available guidelines. Nevertheless, about 50% of physicians still believe that SIT has to be used as a last-choice adjunct when pharmacotherapy fails. Chest physicians are well aware that SIT has a disease-modifying effect, in addition to its short-term clinical efficacy. Finally, the majority of interviewed specialists agree on the need of getting more information and education on SIT.* ***Conclusions.*** *This survey about the perception of SIT among chest physicians in Italy highlighted a satisfactory overall knowledge of SIT and only few weak points. These results would allow to take appropriate educational actions and this questionnaire could be used to monitor the possible effects of divulgation and educational initiatives over time.*

Introduction

Allergy still remains a major public health concern which has pandemic proportions, affecting more than 150 million people in Europe. Taking into account the epidemiological trends, it is hypothesized that within 15 years more than 50% of the European population will suffer from some type of allergy (1,2). Allergic patients suffer from a debilitating disease, with a major impact on their quality of life (QoL) and work/school performance, and constitute a significant burden on health economics, due to lost productivity and absenteeism (3). Given that allergy triggers such as urbanization, pollution and climate change are not expected to change significantly, the only ways to afford this burden are strengthening and optimizing the preventive and treatment strategies. Nonetheless, it has been repeatedly shown that the available pharmacological treatments are neither capable to achieve a long-term effect once stopped, nor to induce significant immunological changes. On the contrary, allergen-specific immunotherapy (SIT), which is based on the subcutaneous (SCIT) or sublingual (SLIT) administration of high allergen doses, was proven able to reduce asthma/rhinitis symptoms and to achieve a long-lasting effect. However, SIT is currently used only as a second-line treatment, and often suggested as a last-choice. Indeed, in the more recent guidelines and academic position statements, the use of SIT has been advocated for those patients with milder disease, also in order to prevent the progression of allergic respiratory diseases. In fact, the clinical value of SIT has been confirmed in multiple clinical trials and meta-analyses, also improving the patient reported outcomes, such as Quality of Life (QoL), long-term costs, burden of allergies, and effect on the course of the disease (4-6). Despite the aforementioned experimental evidence, SIT is still not receiving an adequate attention from Medical Institutions, as the general underuse of this treatment clearly demonstrates (7). In this context, the partnership and cooperation of different medical subjects (i.e. general practitioners, allergists, pediatricians, chest physicians) would be crucial. In a previous questionnaire-based study we observed that, at least among the Italian GPs, the perception of SIT as a valuable treatment was near to optimal (8). It is true that GPs are primarily responsible for education and information about respiratory allergy and its treatment, but it is also true that pulmonologists are often involved in the primary diagnosis and care of this disease (9). This survey was specifically designed for chest physicians, intended to assess their knowledge on SIT. This was done by a questionnaire-based survey.

Methods

A panel of experts, based on guidelines and literature analysis prepared a questionnaire of 16 points of interest/questions specifically dedicated to chest physician specialists. The questionnaire (Y/N or multiple-choice answers) was subdivided into five main sections (clinical/general aspects, efficacy perception, pharmacoeconomic aspects, SLIT versus SCIT, awareness of guidelines) (see **table 1**). The study, since cross-sectional and observational, did not need an official approval by the Ethic Committee to whom it was simply notified to warrant the privacy of the recorded data. The questionnaires were emailed to 115 specialists in Respiratory Medicine, randomly selected from the databases of the Italian societies of respiratory medicine, and had to be returned anonymously. Only the returned questionnaires of those physicians currently using SIT were taken into consideration. The selection of the chest physicians also took into account the harmonic distribution across the Italian Country, in order to avoid any "bias" connected to different attitudes about SIT. Questionnaires were sent to pulmonologists from the beginning of September to the end of October 2011.

Table 1 *- Number and % of responses to the items in the SIT - pulmonologist questionnaire.*

ITEM	N	%
1. In subjects with respiratory allergies (rhinitis and asthma), do you believe that SIT allergenic extracts may be a valid therapeutic option?		
Yes	73	90
No	8	10
2. Do you give the SIT directly to your patients?		
Yes	53	65
No	16	20
I follow patients when SIT was initiated by another specialist (e.g. allergist)	12	15
3. If so, how many patients come in a year?		
More than 10 patients	36	44.5
Between 5 and 10 patients	20	24.5
Between 1 and 5 patients	25	31
4. In patients dealing with SIT, the decision was taken:		
Not answering	15	18.5
After consulting with allergist	16	20
In total autonomy	50	61.5
5. If using the SIT, which is its main indication?		
Asthma	10	12
Rhinitis plus asthma	50	61.5
Rhinitis	21	26.5

continues...

...continues

ITEM	N	%
6. If administering the SIT, which allergenic extracts do you use?		
Perennial	20	24.5
Seasonal	17	21
Both in equal measure	44	54.5
7. Which schedule does the patient usually follow (pre-coseasonal, continuous, continuous for seasonal forms also)?		
Pre-coseasonal	25	31
Continuous	33	41
Continuous for seasonal forms also	23	28
8. In your opinion, SIT is:		
An alternative treatment with respect to pharmacologic therapy	2	2.5
A limited efficacy treatment	4	5
A treatment that can only be used in a small proportion of patients	10	12
The only treatment available	24	29.5
A complementary treatment to drug therapy	41	51
9. Which route of administration do you use primarily?		
Sublingual	50	62
Subcutaneous	11	13.5
Both	20	24.5
10. Which route of administration do you consider clinically superior?		
Effective in equal measure	29	36
Sublingual	21	26
Subcutaneous	31	38
11. How long do you continue the SIT treatment?		
5 or more years	16	20
3 years	60	74
1 year	5	6
12. Can SIT modify the natural history of the respiratory allergic disease?		
Yes	65	80
No	16	20
13. Which of the following statements do you believe is the most significant?		
SIT may reduce the risk of new sensitizations	8	10
SIT is effective in reducing the use of medications	16	20
SIT may reduce the risk of asthma	21	26
SIT is effective in reducing allergic symptoms	36	44
14. In a symptomatic asthmatic patient, do you continue to administer SIT?		
No	7	8.5
Yes	21	26
Only after having checked the symptoms with anti-asthma drugs	53	65.5
15. Would you like to receive more information about SIT (meetings/respiratory medicine journals)?		
Yes	74	91.5
No	7	8.5
16. Is SIT mentioned in asthma/rhinitis guidelines, as GINA and ARIA?		
Yes, in both	64	79
No	5	6
Only in ARIA guidelines	9	11
Only in GINA guidelines	3	4

Results

Among the 115 interviewed chest physicians, 90 (78%) responded as users of SIT, and 81 were fully analyzed (9 were inadequately completed). The respondent population had a mean age of 51 years (range 33-63, 74% male). The pneumologists were distributed as follows: 62 worked in hospital, 12 on the territory, 5 were private practitioners, and 2 worked into a University setting. The distribution on the national territory was the following: Northern Italy 29%, Central Italy 34%, and Southern Italy 37%.

According to the results (shown in **table 1**), it seems that the general knowledge on SIT is overall satisfactory among pulmonologists, and that they are well aware that SIT is recommended in the most diffused guidelines (item 16). Nevertheless, a relevant proportion of chest physicians (> 50%) still believe that SIT is an adjunct to pharmacotherapy, to be used only when drugs fail to control asthma. This may be the result of the statements reported in previous guidelines such as GINA. Also, chest physicians are well aware that SIT has a disease-modifying effect in addition to the short term clinical efficacy (item 12). The main differences between sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT), especially concerning the efficacy aspects, are known as well. Importantly, the majority of Italian chest physicians herein involved agree on the need to improve the cooperation with other specialists, and auspicate to get more information and education on the specific aspect of SIT, for instance in scientific meetings (item 15). Due to the cross-sectional design of the study, no specific investigation on adherence, outcomes or functional approaches could be done.

Discussion

Among the treatments currently available for respiratory allergy (including allergen avoidance and pharmacotherapy) SIT is the only approach capable to act not only on the symptoms, but also on the immunologic aspects. In fact, more than 200 trials have confirmed its efficacy and safety (both for SCIT and SLIT) in allergic rhinitis and asthma (10). Current available data give solid evidence on the clinical efficacy of both SCIT and SLIT in allergic rhinitis and asthma. SIT is the only treatment that causally addresses IgE-mediated immunopathology and modulates the natural course of the disease (11-14). Furthermore, SIT has been shown to prevent the progression of the disease and the onset of new sensitizations and asthma long after it was discontinued.

The current burden of allergic diseases, estimated by both direct and indirect costs, is very relevant. In fact the cost estimation for rhinitis amounts globally to 4-10 billion dollars/year in the U.S. and to an average annual cost of 1089 euros per child/adolescent and 1543 euros per adult in Europe. The estimated annual costs in Northern America for asthma amounted to 14 billion dollars. Consequently, preventive strategies aimed at reducing the clinical severity of allergy are potentially able to reduce its costs. Among them, SIT joins to the preventive capacity the carryover effect once treatment is discontinued. Several studies, conducted in different Countries confirmed a favorable cost-benefit balance (15-16).

In previous surveys among Italian GPs about the modality of use of SIT (17,18) we found that: a) physicians are overall familiar with SIT and most recommendations of the guidelines are observed; b) the majority of physicians perform SIT in a hospital environment; c) the availability of resuscitation facilities and/or drugs to treat possible severe reactions is still not optimal; d) a poor attention is paid to the education of the patients (17). It is true that GPs remain the primary responsible for education and information when SIT is prescribed, and their cooperation with specialists in managing allergies is auspicated; it is also true that chest physicians are often involved in the diagnostic process concerning asthma/rhinitis, since they intercept many patients suffering from respiratory allergy. Thus, we performed a specifically designed survey to assess the level of knowledge about SIT among chest physicians. This survey, designed to evaluate the perception of SIT among chest physicians, was established to assess their knowledge on SIT. Among the interviewed pulmonologists, 78% use SIT. According to the respondents' opinion, they are well aware that SIT is recommended in the most diffused guidelines. Nevertheless, a relevant proportion of pulmonologists believe that SIT should be an adjunct to pharmacotherapy to be used as a last choice. This may be the result of the statements reported in previous guidelines such as GINA (19). Also, chest physicians are overall aware that SIT has a disease-modifying effect in addition to the short-term clinical efficacy. The main differences between SLIT and SCIT, especially those concerning the efficacy aspects, are known as well. A special point of this survey is that, for the first time, SLIT was specifically investigated in a pneumological area of expertise.

Importantly, the majority of pulmonologists agree on the need to improve the cooperation with other specialists, and express the auspice to get more information and education on the specific aspect of SIT, for instance in scientific meetings. In conclusion, our survey about the perception of SIT among Italian chest physicians highlighted a satisfactory overall knowledge of SIT and only few weak points. These results would allow to take appropriate educational actions and this questionnaire could be used to monitor the possible effects of divulgation and educational initiatives over time.

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N. Santos[1], V. Iraola[2], J.L. Plácido[1]

Tetranychus urticae allergy in a population without occupational exposure

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Key words

Tetranychus urticae*; spider mite; conjunctival provocation test; allergy*

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Summary
Background. Tetranychus urticae *is a phytophagus mite found in the leaves of numerous plants. High sensitization rates have been demonstrated, however, provocation tests have only been performed in an occupational setting.* ***Objective.*** *To assess accuracy of skin prick tests and clinical relevance of* T. urticae *sensitization by means of conjunctival provocation tests (CPT) in a population without occupational exposure and to evaluate possible environmental risk factors for* T. urticae *allergy.* ***Methods.*** *Patients ≥ 18 years old sensitized to* T. urticae *(n = 12) and a non-sensitized control group (n = 12) were invited to perform CPT with* T. urticae *and fulfill a questionnaire including demographic data, questions on environmental exposure to* T. urticae *and allergy symptoms/diagnosis. A single-blinded placebo-controlled CPT with* T. urticae *(Leti®) was performed with increasing concentrations (0.002, 0.02, 0.2 and 2 mg/mL) and considered positive if conjunctival hyperemia, palpebral edema or lacrimation were observed in the tested eye.* ***Results.*** *Of* T. urticae *sensitized patients (mean wheal 4.4±1.5 mm), 9 had a positive CPT, including 3 monosensitized. A good diagnostic accuracy was found for skin prick tests: AUC = 0.952, sensitivity = 100%, specificity = 80%, positive likelihood ratio = 5 and negative likelihood ratio = 0 for a 3 mm wheal. No differences were found between allergic and non-allergic subjects regarding atopy, allergic disease or farming activities.* ***Conclusions.*** *A high prevalence of allergy to* Tetranychus urticae *was found in the north of Portugal. Future studies with a larger number of patients are needed to evaluate its relation to clinical symptoms and the impact of environmental factors.*

Introduction

Tetranychus urticae, commonly known as red spider mite or two-spotted spider mite, is a macroscopic phytophagus mite of the *Acari* subclass and *Trombidiformes* order, found in the leaves of numerous plants and an important plague in agriculture, especially in association with sulfur pesticides utilization, to which it is specially resistant (1).

A high sensitization rate to this mite has been shown both in occupational (2) and non-occupational exposure (3), and both species specific and cross-reactive allergens with house dust mites have been identified (4,5).

In Portugal, predominantly in the North of the country, viticulture, farming and greenhouses are important economic activities, and we have previously reported that almost 40% of patients followed in the Immunoallergy Department of our University Hospital were sensitized to *T. urticae* (6). However, the clinical relevance of this sensitization was not assessed.

Allergy to *T. urticae* has been associated with symptoms of rhinitis in the summer and autumn, asthma, contact dermatitis and

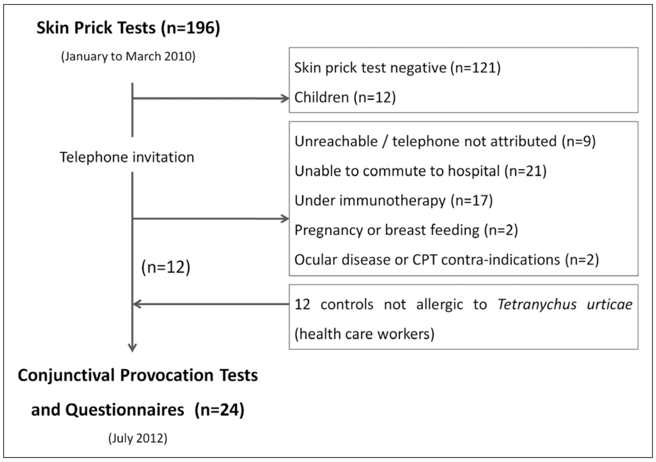
urticaria (3,7,8), and was previously evaluated with bronchial (9,10), and environmental provocation (8), but not with other safer and simpler target organ provocations, namely nasal or conjunctival provocation tests.
Our aims were to assess accuracy of skin prick tests and clinical relevance of *T. urticae* sensitization by means of conjunctival provocation test (CPT) in a population without known occupational exposure to this mite and to evaluate possible environmental risk factors for *T. urticae* allergy.

Methods

Study design and participants

Subjects aged 18 years or older who participated in a previous study to determine sensitization frequency to *T. urticae* (6) and had a positive skin prick test, were eligible (**figure 1**).

Figure 1 *- Study protocol and patients excluded.*



Subjects were contacted by telephone and invited to participate in the study, consisting on a skin prick test to *T. urticae* to assess wheal size, a CPT and a questionnaire on allergy symptoms and risk factors for *T. urticae* exposure.
Those to whom the phone number was no longer attributed, who did not answer the telephone after 3 attempts, who could not commute to the hospital in one of the four days set to perform the study, who were under current or previous allergen specific immunotherapy with mites, who were pregnant, breastfeeding or presented any contra-indication for CPT, were excluded.
A control group of medical, nursing and technical personal of the Immunoallergy Department of Centro Hospitalar São João, E.P.E., consisting of atopic and non-atopic subjects not sensitized to *T. urticae* was also recruited.
24 patients were included, 20 (83.3%) female, mean (SD) age 32.8 (10.9) years old, ranging from 19 to 54 years old.
This study was approved by the ethics committee of Centro Hospitalar São João, E.P.E. Written informed consent was obtained from all subjects included.

Skin prick tests

Skin prick tests were performed with an extract of *T. urticae* bodies (Leti©) 2 mg/mL, histamine 10 mg/mL and a saline solution as negative control. The procedure was performed by the investigator. Extracts were applied in the volar surface of the forearm and pricked with an allergen prick lancet (Heinz Herenz Medizinalbedarf GmbH©), according to international recommendations (11). The mean wheal size was measured and registered. Subjects were considered sensitized if a mean wheal diameter ≥ 3mm for *T. urticae* was observed after 15 minutes.
Other sensitizations, as for house dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*), storage mites (*Lepidoglyphus destructor*, *Tyrophagus putrescentiae* and *Acarus siro*), cat and dog dander, pollen (*Platanus acerifola*, *Betula verrucosa*, *Olea europea*, grass mix, *Parietaria judaica, Plantago lanceolata* and *Artemisia vulgaris*) and fungi (*Alternaria*, *Cladiosporum*, *Aspergillus* and *Penicillium*) were evaluated according to the results obtained in our previous study (6), using the same methodology.

Conjunctival provocation test (CPT)

A single-blinded placebo-controlled CPT with *T. urticae* was performed, according to the Allergy Department's protocol (12). Exclusion criteria were ocular infection, dry eye syndrome, autoimmune disorders and allergic conjunctivitis exacerbation. Subjects were instructed to stop any topical eye drugs 2 weeks before, oral or nasal corticosteroids 2 weeks before, oral antihistamines 1 week before and not to wear contact lenses on CPT day. Subjects who could not stop medication were also excluded.
Four concentrations of *T. urticae* were prepared from the original lyophilized 2 mg/mL extract (0.002, 0.02, 0.2 and 2 mg/mL) according to manufacturer's instructions and used in the 24 hours following preparation.
One single drop of increasing concentration was applied in the conjunctival eye sac, while a control solution of diluent was applied in the opposite eye. The eyes were evaluated after 10 minutes of each concentration.
The CPT was considered positive if objective signs of conjunctival hyperemia, palpebral edema or lacrimation were observed in the tested eye. Patients with positive tests did not proceed to the next concentration and were treated with a topical antihistamine (opatanol 1 mg/mL) and eventually topical corti-

costeroid (rimexolone 10 mg/mL) until full recovery. The test was negative if no reaction was observed 10 minutes after the last concentration. Patients were instructed to inform if any late reaction occurred.

Questionnaire

Subjects filled in a questionnaire including demographic data, questions on hypothesized risk factors for environmental exposure to *T. urticae* and allergy symptoms/diagnosis.

Questions on environmental exposure included housing type (apartment or dwelling house, with or without a garden), region (rural or urban), distance to farming fields or greenhouses, and farming activities, either professional or recreational (mean hours per week spent, mean years, type of cultures exposed to and pesticide use).

In patients presenting with allergy symptoms, a relation with either exposure or removal from those factors was asked and the most symptomatic seasons of the year were also questioned.

Statistic analysis

Categorical variables were described using absolute and relative frequencies; comparisons were performed with Qui-square or Fisher's exact tests. Continuous variables were described using mean with standard deviation (SD); comparisons were performed with independent samples T-test. A p-value of < 0.05 was considered statistically significant.

Diagnostic accuracy of the *T. urticae* skin prick test was presented as sensitivity, specificity and positive and negative likelihood ratios with 95% confidence intervals. Spearman correlation test was used to test association between mean wheal size and the CPT result. The Area Under Curve (AUC) of the test was calculated.

Data analyses were performed using SPSS® version 18.0 for Mac (IBM SPSS, Chicago, USA) and VassarStats® online calculator (13) for diagnostic accuracy tests.

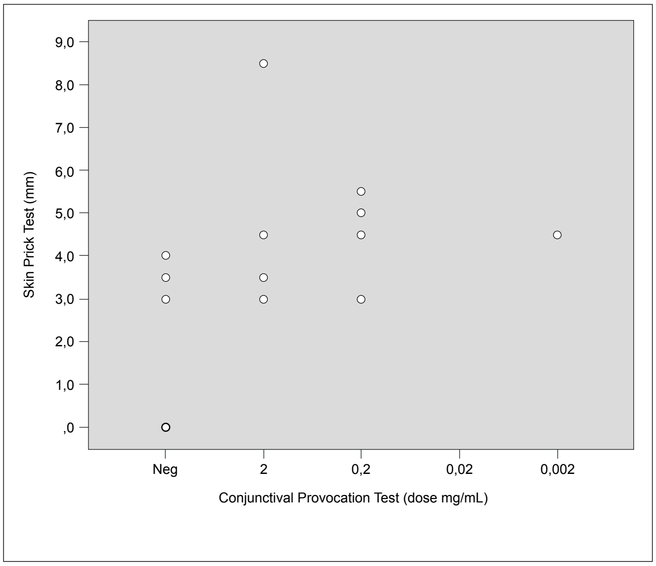
Results

Among the 24 subjects included, 12 were sensitized to *T. urticae* and 12 were controls; their clinical and demographical characteristics are presented in **table 1**.

The sensitized subjects had a mean (SD) wheal size of 4.4 (1.5) mm and included 3 monosensitized patients.

Figure 2 shows the relation between wheal size in mm and CPT result, including the dose that elicited the positive response. The Area Under Curve (AUC) for the skin prick test with *T. urticae* was of 0.952. For a wheal size ≥ 3 mm, the test presented a sensitivity of 100% (63-100%), specificity of 80% (52-95%), positive likelihood ratio of 5 (1.8-13.8) and negative likelihood ratio of 0 (0-not applicable). Three false positive patients had positive skin prick tests to *T. urticae* (wheals measuring 3-4 mm) but negative CPT to *T. urticae*, were co-sensitized to mites, 2 had rhinitis and the other referred asthma and urticaria symptoms. Considering a wheal size ≥ 4.5 mm, the false negatives were excluded, giving a specificity of 100% (75-100%). The correlation between wheal size and CPT eliciting dose was not significant (r = -0,112. p = 0,774). In all patients, positive CPT symptoms resolved within 30 minutes after topical antihistamine treatment, and none reported late reactions.

Figure 2 *- Scatter plot showing the relation between skin prick test wheal size and conjunctival provocation test result, including eliciting dose.*



No differences were found between subjects positive and negative to the CPT regarding atopy, allergic disease, housing type, region type, distance from farming fields or greenhouses, and farming activities (**table 2**). None worked in agriculture or other professions with known occupational exposure to *T. urticae*.

Seven patients with positive CPT to *T. urticae* referred respiratory symptoms: 6 reported symptoms in the spring (2 of these were co-sensitized to pollen), 2 in the summer, 4 in the autumn and 4 during winter; 5 referred an exacerbation of symptoms in the vicinities of farming fields (3 were co-sensitized to pollen); 1 monosensitized patient had rhinitis all year long, noticing however an exacerbation while in the countryside.

Two patients monosensitized to *T. urticae* reported isolated cutaneous symptoms (urticaria) in the spring, which was not related either to exposure or to removal from farming fields or greenhouses.

Sensitization to *T. urticae*	**Yes (n = 12)**	**No (n = 12)**	**p (< 0.05)[1]**
Age, mean (SD)	28.8 (9.9)	36.8 (10.8)	0.071
Gender, female (%)	10 (83)	10 (83)	1.000
Co-sensitization, mites (%)	9 (75)	2 (17)	0.012
Allergy symptoms, n (%)	12 (100)	9 (75)	
Rhinitis	9 (75)	6 (50)	0.400
Asthma	3 (25)	3 (25)	1.000
Cutaneous	3 (25)	3 (25)	1.000

[1]Fisher test

Table 1 *- Clinical and demographical data on subjects sensitized to* Tetranychus urticae *and controls.*

Conjunctival Provocation Test	**Positive (n = 9)**	**Negative (n = 15)**	**p (< 0.05)[1]**
Atopy, n (%)	6 (67)	8 (53)	0.678
Allergic symptoms, n (%)	9 (100)	12 (80)	0.266
Rhinits	7 (78)	8 (53)	0.389
Asthma	2 (22)	4 (27)	1.000
Cutaneous	2 (22)	4 (27)	1.000
Housing type, dwelling house (%)	6 (67)	5 (33)	0.206
Region type, rural (%)	6 (67)	5 (33)	0.214
Farming activity, n (%)	3 (33)	7 (47)	0.678
> 40 hours per week	0 (0)	1 (7)	1.000
< 20 hours per week	3 (33)	6 (40)	
Pesticide use	2 (22)	4 (27)	1.000
Distance to farming fields, n (%)			0.590
< 200 meters	5 (56)	6 (40)	
> 1 Kilometer	2 (22)	6 (40)	

[1]Fisher test

Table 2 *- Frequency of atopy, allergic symptoms and evaluated risk factors for* Tetranychus urticae *in subjects with positive and negative conjunctival provocation test.*

Discussion

This is the first study, to our knowledge, to report CPT with *T. urticae* and to perform a specific provocation test in patients without known occupational or environmental exposure to this mite. To evaluate allergy to *T. urticae*, we chose to perform CPT because it is standardized, easy to perform and safer for the patients, and because of our department's experience with the technique (12). CPT has been extensively used for ocular allergy diagnosis (14) but has also the potential to evaluate other allergic diseases, where eye is used as a target organ (15-17).

We were unable to perform a double-blinded CPT due to the difference in color of the higher concentration *T. urticae* solution in relation to the control solution. However, an effort was made to conceal the content from the subjects, and *T. urticae* drops were randomly applied either in the left or right eye of a given patient, so that subjects remained blinded. Also, the CPT was only considered positive when objective signs were observed and these were always found to be associated with pruritus only in the tested eye.

In our study CPT was positive in 9 out of 12 patients sensitized to *T. urticae*. Skin prick tests revealed a good accuracy to detect allergy (AUC = 0.952, sensitivity = 100% and specificity = 80% for a skin prick test wheal size ≥ 3 mm); all patients with wheal size ≥ 4.5mm had a positive CPT and therefore could be con-

sidered allergic without performing a specific provocation test.
In relation to other studies where a provocation test was performed, Astarita et al. (8) evaluated *T. urticae* allergy through a single-blinded specific exposure test, with symptoms and peak expiratory flow rate monitorization, in a pesticide-free oleander greenhouse specifically infested by *T. urticae*; it was positive in all 28 farmers sensitized to *T. urticae* who reported occupational symptoms, inducing the referred respiratory or cutaneous symptoms until 1 hour after exposure. Delgado et al. (9) and Jee et al. (10) evaluated suspected *T. urticae* induced asthma with a specific bronchial provocation test, which was positive in 12 out of 13 carnation greenhouse workers and 10 out of 16 asthmatics living near pear orchards, respectively. Almost half of them presented a late asthmatic response.

Most of our *T. urticae* allergic patients, even without pollen sensitization, reported nasal symptoms in the spring. Although *T. urticae* levels in different cultures peak between July and August and that Astarita et al. (8) reported that recurrent summer-autumn occupational rhinitis showed the best clinical correlation with *T. urticae* in Italian farmers, it has been described that *T. urticae* populations increase in spring in adventitious plants and ground cover vegetation, moving to the cultures in summer (18), which might explain the occurrence of spring symptoms even in patients without pollen sensitization.

Regarding housing type, region type, distance to farming fields or greenhouses, and farming activities, no differences were found between those with and without *T. urticae* allergy. However, we point out that allergy symptoms were self-reported and retrospective, and that assessed risk factors were not confirmed through objective measures of *T. urticae* exposure.

To conclude, a high prevalence of sensitization and conjunctival provocation test confirmed allergy to *Tetranychus urticae* was found in a non-occupational population from the North of Portugal. Future studies with a larger number of patients are needed to evaluate its relation to clinical symptoms and the impact of environmental factors.

The data in this article has been briefly presented in poster form in the EAACI-WAO Congress 2013: Santos N, Plácido JL. Sensitization to *Tetranychus urticae*: prevalence and clinical relevance. Allergy 2013; 68 (Suppl.97):463.

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In patients with LTP syndrome food-specific IgE show a predictable hierarchical order

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Key Words

Food allergy; lipid transfer proteins; specific IgE

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Summary

Background. *Lipid transfer protein (LTP) is a widely cross-reacting allergen in plant foods.* ***Objective.*** *To assess whether IgE to vegetable foods show predictable trends in LTP allergic patients.* ***Methods.*** *Clinical allergy to plant foods other than peach was sought in 15 consecutive peach-allergic adults monosensitized to LTP. IgE specific for peach, apple, hazelnut, walnut, peanut, lentil, maize, soybean, tomato, sesame, mustard melon, kiwi, and celery as well as to mugwort pollen was measured.* ***Results.*** *Peach-specific IgE levels exceeded IgE to all other study foods. The higher were peach-specific IgE levels, the higher was the probability that other plant-derived foods scored positive. Mean IgE levels specific for all study foods were strongly correlated to peach specific IgE. Food-specific IgE followed a rather precise hierarchy, both in terms of number of positive in-vitro tests and of IgE levels, with apple at the second place after peach, followed by walnut, hazelnut, peanut, lentil, maize, soybean, tomato, kiwi, sesame, mustard, melon, and celery. Such hierarchy was not necessarily paralleled by clinical allergy as lentil, maize, and soybean scored positive in the majority of patients, but induced allergy in 0, 1, and 0 patients, respectively. IgE levels were not necessarily correlated with the severity of clinical allergy. Little or no IgE reactivity to mugwort pollen was found.* ***Conclusion.*** *In LTP syndrome, IgE reactivity to foods other than peach is in most cases predictable and follows a regular sequence that probably depends on the degree of homology with Pru p 3. The reasons why some foods are tolerated by most patients despite elevated IgE reactivity remains to be elucidated.*

Introduction

Lipid transfer protein (LTP), the major food allergen in the Mediterranean basin, is widely distributed throughout the plant kingdom. LTPs from distinct plant-derived foods show a moderate to high degree of cross-reactivity, due to a sequence homology ranging between 35% and 95% (1). Most allergists agree that the peach is the primary source of sensitization to this protein, and dominates the immune response to this allergen (2,3), although a possible influence by sensitization to LTP present in some pollens, particularly those of plane tree and mugwort has been suggested (3-5). The clinical spectrum of LTP allergy ranges from patients allergic uniquely to the peach to patients allergic to a large array of fruits and vegetables. Previous studies found that the level of IgE specific for peach LTP, Pru p 3, is critical for the occurrence of cross-reactivity to botanically related (*Rosaceae*) and unrelated plant foods (6,7), although subsequent investigations were unable to detect sharp cutoff levels able to discriminate allergic patients from subjects with clinically irrelevant sensitization (8). However, it has to be considered that the reactivity of the patients varies with the amount of allergen ingested, the affinity of IgE antibodies, the exposure to other allergens, the degree of processing and storage of food stuff. Whether the IgE levels to botanically distinct plant-derived foods show predictable trends in LTP-allergic patients has not been investigated so far. In the present study, IgE specific for several different vegetable foods were measured in parallel in patients sensitized to LTP.

Methods

The study was carried out on sera from 15 consecutive peach-allergic adults (M/F 5/10; mean age 34,2 years, range 19-78 years) seen at the allergy outpatient service of the Clinica San Carlo and diagnosed as being most probably monosensitized to lipid transfer protein. The diagnosis of peach allergy was based on a history of oral allergy syndrome (defined as the occurrence of oral itching with or without angioedema of the lips and/or tongue, some minutes after the ingestion of a food), urticaria with or without angioedema, anaphylaxis, digestive symptoms, and/or respiratory symptoms (rhino-conjunctivitis and/or asthma) following the ingestion of peach associated with an unequivocally positive SPT with fresh peach by the prick-prick technique. The diagnosis of probable monosensitization to LTP was based on positive SPT with a commercial peach extract (ALK-Abellò, Madrid, Spain) in the absence of skin reactivity to a commercial extract of birch pollen (Allergopharma, Rainbeck, Germany; 50 000 SBU/ml) and to a commercial date palm pollen extract enriched in profilin (ALK-Abellò; 50 µg protein/ml), thus ruling out sensitization to the other two main cross-reacting plant food pan-allergens, namely PR-10 and profilin. In previous studies, the commercial peach extract was found to react exclusively to LTP-hypersensitive patients and did not induce any skin reaction in patients sensitized either to Pru p 1, the peach allergen homologous to the major birch pollen allergen Bet v 1, or to Pru p 4, the peach profilin (9). This extract contains 30µg/ml of peach LTP, Pru p 3. The clinical allergy to other plant-derived foods was ascertained by interview using the same criteria defined above. It was also ascertained whether patients ate regularly the foods that they reported to tolerate.

IgE specific for peach, apple, hazelnut, walnut, peanut, lentil, maize, soybean, tomato, sesame, mustard melon, kiwi, and celery was measured in sera from all patients by ImmunoCAP FEIA (Thermo-Fisher Phadia, Uppsala, Sweden) following manufacturer's recommendations. Further, IgE specific for mugwort pollen, a pollen that has been regarded as a possible source of LTP sensitization (3,4,5), was measured. Levels were expressed as kUA/L; levels exceeding 0.35 kUA/L were regarded as positive. The correlation between peach-specific IgE levels and levels of IgE specific for all other study foods was assessed using Pearson's coefficient method. A probability value $< 5\%$ was considered statistically significant.

Since the study was retrospective and based on routine investigations performed on patients spontaneously presenting at the clinic for suspect food allergy, no institutional ethical permission was needed.

Results

IgE measurement results are shown in **table 1**. As expected, all patients scored positive for the peach and peach-specific IgE levels were higher than IgE specific for all other study foods in all patients but two showing high specific IgE levels, in whom apple IgE were slightly higher than peach IgE. Further, the higher were peach-specific IgE levels, the higher was the probability that other plant-derived foods scored positive. In effect, the mean IgE levels specific for all study foods except kiwi were strongly correlated to peach specific IgE levels (correlation coefficient r ranging from 0.814 for peanut to 0.996 for apple; $p < 0.001$ for all foods). Kiwi IgE levels also were statistically correlated with peach IgE levels ($p < 0.01$) but the correlation coefficient was lower ($r = 0.701$). Food-specific IgE followed a rather precise hierarchy both in terms of number of positive in-vitro tests and of specific IgE levels, with apple at the second place after peach, followed by walnut, hazelnut, peanut, lentil, maize, soybean, tomato, kiwi, sesame, mustard, melon, and celery (**figure 1**). The offending foods in study patients are shown in **table 2**. Although clinical allergy was more frequently induced by Rosaceae and nuts, who also showed the highest levels of IgE in most patients, the IgE hierarchy was not necessarily associated with clinical allergy to the single foods; in fact, lentil, maize, and soybean scored positive in the majority of patients but only 1 patient had a history of maize allergy, whereas lentil and soybean were tolerated by all patients, just as was sesame that scored positive in 5 cases. Further, allergen specific IgE levels were not necessarily correlated with the severity of clinical allergy, with patients showing very high specific IgE levels and only local symptoms (e.g., patient # 2 in **tables 1** and **2**), and patients with low specific IgE levels and a history of systemic reactions to foods (e.g., patient # 14 in **table 1** and **2**). Finally, in patient # 7 who had a clinical history of allergy to hazelnut, peanut, tomato, and melon the ImmunoCAP failed, scoring negative for all these 4 foods, in the face of extremely strong reactions on SPT with commercial extracts (mean wheal diameter 8 mm, 11.5 mm, 12 mm, and 15.5 mm, respectively).

IgE reactivity to mugwort pollen was detected in sera from 8/15 patients. In 7/8 cases mugwort IgE levels were by far lower than peach specific IgE (**table 1**). Seven patients did not show any mugwort reactivity.

***Table 1** - Level of IgE to the study foods measured in 15 patients monosensitized to LTP.*

Patients	Peach	Apple	Walnut	Hazelnut	Peanut	Lentil	Maize	Soybean	Tomato	Kiwi	Sesame	Mustard	Melon	Celery	Mugwort pollen
1	58,1	59,2	43,3	7,66	20,9	23	21,9	12,9	7,37	1,92	7,21	2,54	1,07	2	0,61
2	16,6	12	11,1	1,17	0,65	0,82	0	0,39	0	1,18	0	0	0	0	1,03
3	12,1	9,1	4,93	1,12	1,9	0,83	0,79	0,58	0,47	0,68	0	0,49	0	0	1
4	11,6	9,25	4,52	3,05	3,75	2,94	2,23	1,37	1,1	1,1	0	0,42	0	0	1,77
5	11,4	11,9	6,61	6,29	2,05	1,77	3,85	0,75	0,67	2,01	0,71	0	0	0,36	1,81
6	7,04	5,34	4,39	1,86	2,14	0,61	3,92	1,14	2,8	0,76	0,67	0	0	1,08	0
7	4,58	2,57	2,05	0	0	0,37	1,53	0	0	0,41	0	0	0	0	1,05
8	3,81	2,33	1,32	0,49	1,86	1,18	1,73	0,79	1,02	0	0,55	0	0	0	0
9	3,12	1,44	0,38	0	0	0	0	0	0	0	0	0	0	0	0,74
10	2,75	1,92	1,59	1,18	0,86	0,75	0,43	0,47	0	0,74	0,56	0	0	0	0
11	1,75	0,74	0	0	0	0	0	0	0	0	0	0	0	0	0
12	1,44	0,77	0	0	0	0,42	0	0	0	0	0	0	0	0	0
13	1,11	0,84	0	0	0	0	0	0	0	0,83	0	0	0	0	0
14	1,08	0,39	0	0	0	0	0	0	0	0	0	0	0	0	0
15	0,41	0	0	0	0	0	0	0	0	0	0	0	0	0	0,61

Specific IgE values are expressed as kU/L (positive if > 0.35 kU/l). Patients have been ordered on the basis of peach-specific IgE levels.

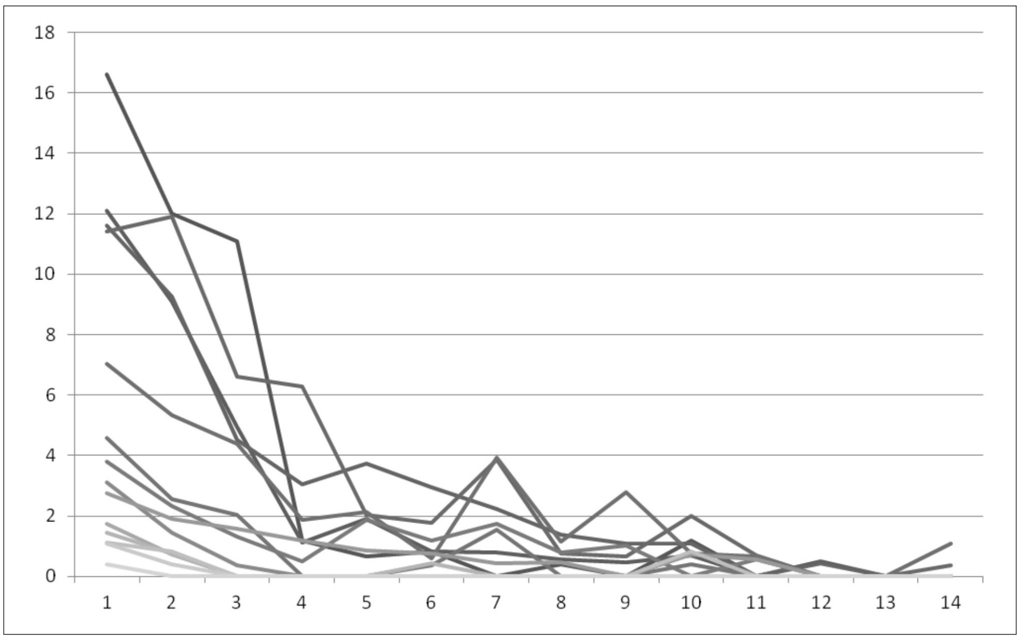

Figure 1** - Specific IgE levels in patients 2-15. Numbers under the horizontal line indicate the study foods (1: Peach; 2: Apple; 3: Walnut; 4: Hazelnut; 5: Peanut; 6: Lentil; 7: Maize; 8: Soybean; 9: Tomato; 10: Kiwi; 11: Sesame: 12: Mustard; 13: Melon; 14: Celery). Numbers along the vertical line are specific IgE levels in Ku/l. Patient # 1 data were excluded due to the excess of specific IgE vs all other patients (see* **table 1).*

Table 2 - *Clinically offending foods in patients with LTP hypersensitivity.*

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	OF
1	X	X					X	X	X	X	X		X		X	X								X	X	X	
2	X				X				X	X	X												X				
3	X							X	X	X	X									X						X	X
4	X	X						X	X	X	X		X				X	X				X					X
5	X								X	X	X			X						X			X		X	X	
6	X	X							X	X			X	X		X				X	X				X		
7	X	X							X	X	X				X	X			X			X					
8	X																										
9	X		X	X					X																		
10	X	X	X						X			X															
11	X	X		X	X		X								X												
12	X		X	X																							
13	X	X																									
14	X		X		X																						
15	X																										

A: Peach; B: Apple; C: Cherry; D: Apricot; E: Plum; F: Pear; G: Strawberry; H: Almond; I: Walnut; J: Hazelnut; K: Peanut; L: Maize; M: Rice; N: Lettuce; O: Kiwi; P: Tomato; Q: Lentil; R: Saffron; S: Melon; T: Pistachio; U: Onion; V: Rucola; W: Cashew; X: Pineapple; Y: Fennel; Z: Other nuts (Brazil nut, coconut, macadamia nut); OF: Other Foods (Bell pepper, Pitaya).
A black box indicates systemic symptoms following the ingestion of a food. A grey box indicates local symptoms (Oral allergy syndrome) and a white box indicates a tolerated food.

Discussion

With the obvious limitations of being retrospective and based on a limited number of patients due to cost problems, this study shows that in patients with lipid transfer protein allergy syndrome, specific IgE levels follow a rather precise hierarchical order. Although this could theoretically be related to the amount of LTP present in the various extract for immunoassay, the possibility that it reflects the degree of homology between the proteins from different botanical sources and the LTP from the primary sensitizer, the peach, seems a more likely explanation. As observed before (3), the higher was the level of IgE to peach LTP, the higher was the likelihood of cross-sensitization to a large number of botanically unrelated plant-derived foods. However, hypersensitivity did not always reflect into clinical cross-reactivity; in fact, for several foods including lentil, soybean, maize and sesame the large majority of patients did not report any clinical reaction despite specific IgE levels that were frequently quite high. This might suggest either that in these foods the protein is less abundant than in the peach, or that it is absorbed more slowly in the gut, or that the thermal processing reduces somehow the allergenicity of this protein in these foods. Both lentil and soybean belong to the *Leguminosae* family, and the good tolerance to legumes by LTP-allergic subjects was already observed several years ago (10). Further, some data suggest that LTP-containing foods may be more harmful if they are ingested alone (11). Finally, although LTP is known as an extremely heat-stable protein (12,13), some data seem to suggest that prolonged heat-treatments at high temperatures may significantly reduce its allergenicity (14). The case of kiwi is somehow special. Recent studies showed that kiwi-allergic patients living in southern Europe are mostly sensitized to profilin or to Act d 10, the kiwi lipid transfer proteins (15). In this study 9/15 patients showed IgE to kiwi, but only 3 patients reported allergic reaction to this fruit and, notably, one of them did not show any IgE reactivity to kiwi both on ImmunoCAP and on SPT, whereas in the remaining 2 specific IgE levels were low. Further, kiwi-specific IgE levels showed a significantly lower correlation with peach-specific IgE than all other study foods, suggesting that either patients were sensitized also to kiwi allergens other Act d 10, or that kiwi LTP shows a rather low homology to Pru p 3 causing a trend in specific IgE that differs from that of all other plant-derived foods. Further studies are needed to elucidate this point.

Regarding the hypothesis that mugwort pollen may represent the primary allergen source for LTP sensitization, the results of the present study seem to rule out this possibility. In fact 7/15 patients did not show any IgE reactivity to this pollen, and in 7 out of the 8 remaining patients mugwort IgE were so much lower than peach IgE to make the hypothesis of a primary airborne, mugwort pollen-driven LTP sensitization unrealistic. Of course, it is possible that these findings are geographically specific for the population studied.

In conclusion, in patients with lipid transfer protein syndrome, IgE reactivity to foods other than peach is in most cases predictable and follows a regular sequence that depends on the degree of homology with Pru p 3. The reasons why some foods are tolerated by most patients despite elevated IgE reactivity remains to be elucidated.

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Middle lobe syndrome: a rare presentation of allergic bronchopulmonary aspergillosis

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Key words

Allergic bronchopulmonary aspergillosis; Aspergillus*; bronchial asthma; central bronchiectasis; middle lobe syndrome*

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Summary

Allergic bronchopulmonary aspergillosis (ABPA) is a disease predominantly seen in susceptible asthmatic subjects, due to a hypersensitivity phenomenon caused by colonisation of the airways by Aspergillus *species. Although collapse, both lobar and segmental due to mucoid impaction, is not uncommon in ABPA, a middle lobe syndrome (MLS) secondary to ABPA is rather an uncommon association. We report this rare and unusual clinical presentation in a 36-year-old male, who presented for evaluation of a "non resolving pneumonia". Imaging suggested the presence of a MLS and central bronchiectasis. Further investigations revealed that the patient met 6/8 of the essential diagnostic criteria for ABPA. Appropriate therapy with oral corticosteroids resulted in remarkable symptomatic improvement.*

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is an immunologically-mediated lung disease occurring in susceptible patients with asthma and cystic fibrosis who develop hypersensitivity to the colonised *Aspergillus* species in the airways, especially *A. fumigatus*. This potentially destructive lung disease has a worldwide distribution and affects approximately 2% of patients with asthma (1). A middle lobe syndrome (MLS) is a clinical entity characterised by chronic or recurrent collapse of the right middle lobe. This term was coined by Graham et al. (2) in 1948, when they described 12 patients with middle lobe atelectasis due to enlarged lymph nodes of non-tuberculous origin. This description followed the original report by Brock and colleagues (3) in 1937, who described eight patients with recurrent atelectasis of the right middle lobe due to extrinsic compression by enlarged tuberculous lymph nodes. Even today, MLS caused by tuberculous lymph nodes is popularly called a "Brock's syndrome".

Radiologically, ABPA is a very "picturesque" disease and has protean manifestations (4). Collapse, both lobar and segmental (5), caused by proximal occlusion of the bronchi by mucoid impaction is not uncommon in ABPA, but a MLS caused by this clinical entity is rather rare and to our knowledge has been documented only twice before (6,7). We report a young man with ABPA who presented with a MLS.

Case Report

A 36-year-old man, a never smoker, was referred for evaluation of a "non-resolving pneumonia". He had a childhood history of episodic wheezing dyspnoea and productive cough, which was associated with recurrent sneezing along with rhinorrhoea. In spite of stains and cultures being negative for *Mycobacterium tu-*

berculosis, the patient had received two complete courses of antituberculous therapy based on his clinical profile. Despite this, there was no resolution of either the symptoms or the opacity for which he was referred. On presentation, he complained of chest pain for the last 15 days along with aggravation of other symptoms. No co-morbidities were reported by the patient and there was no significant family history. Physical examination revealed a young man in no acute distress with no cyanosis or clubbing. Bilateral polyphonic rhonchi with bibasilar coarse crepitations were audible on auscultation. The haemoglobin level was 15.8 gm/dl, along with a total leucocyte count of 11,200 cells/mm^3, with a differential count of neutrophils 70%, lymphocytes 17%, monocytes 1% and eosinophils 1.5%. The absolute eosinophil count was 200 cells/mm^3. On pulmonary function testing, FVC was 3.34 L (76% predicted), FEV_1 was 1.44 L (39% predicted) and FEV_1/FVC ratio was 43% (51% predicted). The total lung capacity was 5.84 L (99% of predicted), residual volume was 2.42 L (157% of predicted) and RV/TLC was 41% (164% of predicted). After inhalation of 400 µg of salbutamol, the FVC was 3.49 L (80% of predicted) and FEV_1 was 1.66 L (45% of predicted). This was indicative of severe airflow limitation with moderate air trapping, and significant reversibility was observed with bronchodilators. Chest radiograph showed an ill-defined opacity abutting the right cardiac border with loss of cardiac silhouette, which appeared as a MLS on the lateral view (**figure 1A** and **1B**). Computed tomography (CT) of the thorax with high resolution cuts (HRCT) confirmed the MLS and, in addition, revealed central bronchiectasis characterised by a 'string of pearls' appearance (**figure 2A** and **2B**), a feature pathognomonic of ABPA (8) prompting further investigations. Skin prick test with antigens of *A. fumigatus* and *A. flavus* elicited a strong type I reaction, whilst strong bands of serum precipitins were detected against the same antigens. Total serum IgE levels were elevated (1,708 kU/L) while specific IgE and IgG were positive for *A. fumigatus*. However, sputum for pathogenic fungi, *M. tuberculosis* and other aerobic organisms were negative. CT of the paranasal sinuses showed left sided anterior, posterior ethmoidal, maxillary and sphenoidal polypoidal sinusitis, but allergic *Aspergillus* sinusitis (AAS) could not be confirmed as the patient refused to undergo functional endoscopic sinus surgery for the diagnosis.

The diagnosis of ABPA was based on: a) presence of asthma; b) type I hypersensitivity to extracts of *A. fumigatus* and *A. flavus* as evidenced by a positive skin prick test; c) elevated total serum IgE levels; d) presence of serum precipitins against *A. fumigatus* and *A. flavus*; e) presence of specific IgE against *A. fumigatus*; f) presence of specific IgG against *A. fumigatus*; and g) central/proximal bronchiectasis on the HRCT scan of the thorax. Our patient met 6/8 of the major diagnostic criteria (**table 1**). A diagnosis of ABPA presenting as a MLS was made, and the patient was initiated on oral prednisolone in the dosage of 0.5 mg/kg daily, which was further tapered at the rate of 5 mg per month over the next 4 months, as the patient improved steadily. In addition, for the management of asthma and rhinosinusitis, he received combination of inhaled budesonide and formoterol, along with intranasal mometasone. Within a fortnight he was, to a large extent, relieved of his symptoms. His complaints of cough and breathlessness had decreased significantly, while wheezing was abolished. Spirometry after 4 months of initiation of therapy with oral corticosteroids for ABPA showed an improvement of 300 mL in FEV_1, and the total IgE levels had reduced by 43% to 976 kU/L. However, the chest radiograph continued to depict the middle lobe opacity despite the patient being asymptomatic on tapering doses of oral prednisolone.

Figure 1A *- Chest radiograph PA view showing an ill-defined opacity abutting the right cardiac border, with loss of cardiac silhouette suggestive of a middle lobe syndrome.*

Figure 1B *- Lateral view showing wedge shaped antero-inferior opacity confirming a middle lobe syndrome.*

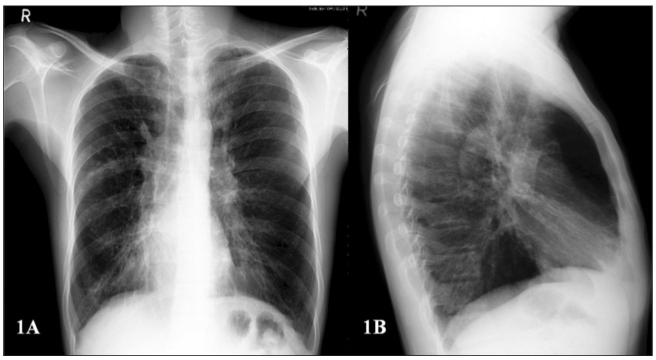

Figure 2A *- Computed tomography of the thorax (mediastinal window) showing collapse of the right middle lobe.*

Figure 2B *- High resolution computed tomography of the thorax, showing central bronchiectasis.*

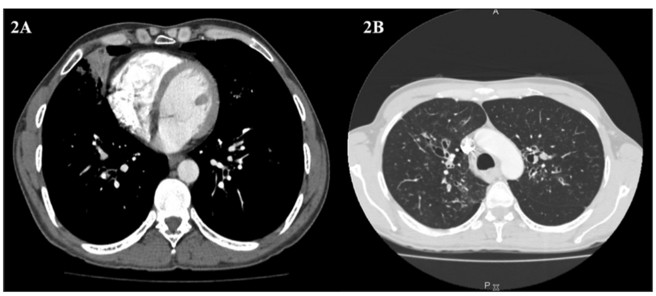

Table 1 *- Comparison of the two previously documented patients, along with the current patient with ABPA presenting with middle lobe syndrome (MLS).*

Authors, Reference **Year of publication, Country**	**Eisenberg RS and Valdesuso C (6)** **1980, USA**	**Shah A et al. (7)** **1993, India**	**Current patient**
Age / Gender	16 years / Female	55 years / Male	36 years / Male
Duration of asthma	No information	2 years	Since childhood
Duration of present illness	5 days	2 weeks	2 weeks
Current symptoms Chest pain Cough Fever	 Yes No Yes	 Yes Yes Yes	 Yes Yes No
Received antituberculous therapy for radiographic appearances	No	Yes	Yes
Peripheral blood eosinophilia	Yes	Yes	No
Transient pulmonary infiltrates (chest radiograph)	Yes	Yes	Serial radiographs not available
Immediate cutaneous reactivity to *Aspergillus*	Yes	Yes	Yes
Elevated total serum IgE	Yes	No information	Yes
Elevated specific IgE and IgG against *A. fumigatus*	No information	No information	Yes
Precipitating antibodies against *A. fumigatus*	Yes	Yes	Yes
Central bronchiectasis with normal tapering of distal bronchi	Yes	Yes	Yes
Expectoration of golden brownish sputum plugs	No	Yes	No
Positive sputum culture for *A. fumigatus*	No	No	No
Late (Arthus type) skin reactivity to *A. fumigatus*	Yes	Yes	No
Concomitant allergic *Aspergillus* sinusitis	No	Yes	No
Response to oral prednisolone	- Marked clearing of the opacity within 2 months	- Symptoms abolished within 2 weeks - Reinflated middle lobe after 1 month	- Significant symptomatic improvement at 2 weeks - Spirometry: improvement at 4 months - Total IgE: 43% reduction at 4 months - MLS persisting at 4 months

Discussion

Middle lobe syndrome is a distinct though uncommon clinical entity, which is rather poorly defined in the literature. Although no consistent clinical definition exists till date, a MLS is often referred to as the chronic or recurrent collapse of the right middle lobe. It is now recognised that several clinical entities can present as MLS (9), a few of them being described as case reports (10,11). One among these uncommon presentations is the occurrence of a MLS in patients with ABPA. Middle lobe syndrome is generally divided into obstructive and non-obstructive types. Obstruction of the middle lobe bronchus may be due to an intraluminal or extraluminal obstruction, and is the characteristic feature of MLS (9). There are several causative factors, which include both benign and malignant conditions. Tumours, including primary carcinoma of the lung, account for 24% of patients with MLS and 8 to 10% are secondary to tuberculosis (Brock's syndrome) (12). The non-obstructive form is typically caused by inflammation, commonly as the result of infection in majority of patients with MLS. Benign inflammatory disease accounts for around 62% of cases and has been identified as the most common cause of MLS (12). It can occur in adults and children with recurrent pneumonia, and is often associated with asthma, bronchiectasis and cystic fibrosis (9).

It has been postulated that the middle lobe has a greater tendency to collapse, as the middle lobe bronchus has a narrow origin with an acute angle, which can easily be obstructed. Furthermore, if the surrounding lymph nodes are enlarged either due to inflammation or a tumour, extrinsic compression can occur. In addition, the anatomical separation of the middle lobe from the right upper and lower lobes by fissures can result in poor collateral ventilation from the surrounding areas (13).

Imaging plays a key role in the diagnosis of MLS. It is now recognised that the atelectatic middle lobe is classically seen on a lateral chest roentgenogram as a wedge-shaped density extending from the hilum, anteriorly and inferiorly (14). Though difficult to detect on a posteroanterior radiograph, the volume loss within the right middle lobe is often seen as obscuring the right cardiac border (Silhouette sign) due to the loss of contact of the right middle lobe with the lateral wall of the right atrium (9). However, when the signs of middle lobe collapse are equivocal, a lordotic view could be of help. In this view, the MLS results in a wedge shaped density in the basal central zone of the right lower lung field, due to parenchymal involvement of the middle lobe (15). The advent of HRCT has helped with the diagnostic confirmation of MLS. It presents as a trapezoidal or broad triangular opacity, which has its base towards the hilum and is contiguous with the right cardiac border. CT imaging can also evaluate endobronchial or parenchymal abnormalities (8), as well as demonstrate bronchiectasis, as was seen in our patient. Bronchial patency, lymph node enlargement and calcifications or other causes of extrinsic compression of the right middle lobe airway too can be visualised (9).

Our patient met 6 of the 8 essential diagnostic criteria for ABPA, including central bronchiectasis, a *sine qua non* (16) for the diagnosis. This was detected on HRCT, done to evaluate MLS. Mucous hypersecretion, commonly seen in patients with asthma, is a well recognised feature of ABPA. Secretions and viscid sputum result in the mucoid impaction and consequent collapse. Ineffective clearance of this impacted mucous along with anatomically poor collateral ventilation of the middle lobe contribute to the development of chronic infection and atelectasis. Due to the vicious cycle of recurrent inflammation and obstruction, leading to a greater impairment of the cough mechanism and expectoration of secretions, these patients are at a greater risk for recurrent collapse of the middle lobe bronchus. While reviewing 1340 chest radiographs in 113 patients with ABPA, lobar/segmental collapse was observed in 17% patients (17).

The comparative features of the two published reports of MLS in ABPA along with the current patient are summarised in **table 1**. The duration of the presenting illness was brief in all the three patients. Symptomatic improvement with oral corticosteroids was observed in all. Although radiological clearance was found in the first two patients, the chest radiograph of the current patient continued to show MLS. Both our patients (cases 2 and 3) had received antituberculous therapy prior to being referred to us for evaluation. In high tuberculous prevalence countries, patients with ABPA are often erroneously diagnosed as pulmonary tuberculosis due to the strikingly similar chest radiograph appearances. This often results in initiation of antituberculous drugs while lung damage continues to progress (16).

The middle lobe has a propensity to collapse in isolation while in ABPA, segmental or lobar collapse is not uncommon. It is rather surprising that a search of the literature revealed only two previous reports of ABPA presenting MLS (6,7). Since the MLS is first detected on imaging, a high index of suspicion would obviate the need for invasive diagnostic procedures like fibreoptic bronchoscopy, that these patients often undergo. ABPA should be considered among the differentials while evaluating a MLS, especially in patients with history suggestive of bronchial asthma.

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Prurigo simplex subacuta or prurigo simplex acuta?

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Key words

Prurigo simplex subacuta; prurigo simplex acuta; childhood

Summary

Prurigo is a condition of nodular cutaneous lesions that itch intensely. Prurigo lesions are divided into acute, subacute and chronic forms that itch intensely. Subacute prurigo (SP) clinically presents as excoriated papules mostly in a symmetrical distribution on the extensor surfaces of the extremities, neck, lower trunk, and buttocks. It tends to occur in middle-aged patients, especially in women. Herein, we described prurigo simplex subacuta in a 4-year-old boy. It was histopathologically documented.

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Introduction

The lesions of prurigo simplex subacuta may be disseminated, or they may be acneiform, or localised on the extremities only (1). Prurigo denotes of a papular and⁄or nodular condition that itches intensely. Clinically, it appears as excoriated papules mostly in a symmetrical distribution on the extensor surfaces of the extremities, neck, lower trunk, and buttocks. It predominantly affects middle-aged women, and may be associated with internal disorders such as diabetes mellitus and atophy, and renal as well as liver insufficiency appears to exist (2-6).

Case report

A 4-year-old boy presented with a 2-month history of intense pruritus and excoriated papules on trunk and extremities. On physical examination, some of the excoriating erythematous lesions, crusted papules, and small nodules were found predominantly on the abdomen and on lower extremity, especially below the knee (**figure 1**). There was no difference between day and night symptoms, no connection to foods, drugs, bite of insects, and other family members had no similar symptoms. In medical history he had no endogenous (e.g. diabetes mellitus, hypertension) or skin diseases (e.g. atopic dermatitis). Laboratory blood investigation revealed normal level of IgE; 28.8 (0-90 iu/mL) and eosinophilia (5.7%, 490 eosinophils/mm^3). 23 parameters skin prick test was negative. A skin punch biopsy was performed from the abdominal lesions, and histopathologic examination showed hyperkeratosis and parakeratosis covered with stratified squamous epithelium skin tissue fragment, perivascular mononuclear cells infiltrates, proliferation of vascular endothelial, and also extravasated erythrocytes in the upper dermis. Toluidine blue staining showed that number of the mast cells was within the normal histological range (**figure 2**). The diagnosis was prurigo simplex subacuta. The patient was observed for several months with antihistamines and topical treatments, and clinical improvement was seen. With this treatment, skin lesions started to heal and pruritus decreased considerably.

Figure 1 *- Excoriated erythematous lesions and crusted papules on lower extremity.*

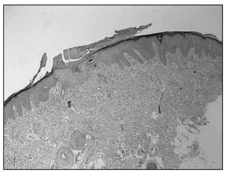

Figure 2 *- Skin punch biopsy, lesional histopathologic examination, hyperkeratosis and parakeratosis covered with stratified squamous epithelium skin tissue fragment. Perivascular mononuclear cells infiltrates, proliferation of vascular endothelial, also extravasated erythrocytes in the upper dermis.*

Discussion

Subacute prurigo, a term more commonly used in Europe and Japan, is a group of similar diseases: prurigo simplex subacuta, "itchy red bump" disease, and Rosen's papular eruption in black men. It tends to occur in middle-aged patients, especially in women, who present comorbidity with psychiatric disorders and emotional overlap (5). Increased numbers of mast cells, Merkel cells and proliferation of sensory nerve fibres found in affected skin may together be responsible for the abnormal perception of itch and touch (7). Sometimes SP was seen with internal diseases such as diabetes mellitus, hypertension and/or renal disease (8). Prurigo simplex subacuta is characterized by intensely pruritic, erythematous urticarial papules. Some patients may have an atopic background or may exhibit dermographism (3). Exogenous toxic factors such as parasites, bacteria, topically or orally administered drugs deposited on the skin can induce itching (9). In our case, there was no history for insect bites, bacterial and parasitic toxic factors. In literature, a subacute prurigo variant of bullous pemphigoid that clinically resembles subacute prurigo was described (10). Differential diagnosis of prurigo simplex subacuta is prurigo simplex acuta (insect bites), dermatitis herpetiformis (can be excluded by the absence in prurigo simplex of neutrophilic microabscesses at the tips of dermal papillae and neutrophils, eosinophils, and nuclear dust in the dermal infiltrate), subacute eczematous dermatitis, urticarial bullous pemphigoid (3), dermatographism / physical urticaria (5). Our patient had no evidence of systemic disease or exogenous factors, and prurigo simplex acuta and dermatitis herpetiformis were excluded. Clinically as well as histopathologically prurigo simplex subacuta was proven, and we couldn't find any underlying etiology. We accepted that it was idiopathic prurigo simplex subacuta.

We would like to draw attention on prurigo simplex subacuta, which should be considered in the differential diagnosis of prurigo simplex acuta (insect bites), which was seen common in children.

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Diagnosis of eosinophilic esophagitis in an infant undergoing milk oral immunotherapy - a case report

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Key words

Eosinophilic esophagitis; oral immunotherapy; cow's milk hypersensitivity; food hypersensitivity; eosinophilia; late-onset hypersensitivity

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Summary

Although the standard of care for cow's milk (CM) allergy is strict food avoidance, oral immunotherapy (OIT) is being widely investigated as an alternative management option in certain cases. Immediate adverse reactions to OIT have been described, but its long-term effects are much less often reported.
We present the case of a girl diagnosed with IgE-mediated CM allergy that was proposed for our CM OIT protocol at the age of 3 years. The first sessions (dose escalation up to 5 ml) were well tolerated, however eight hours after her daily morning dose of 5ml CM the child developed late episodes of vomiting. No other symptoms, particularly immediately after CM ingestion, were reported. These episodes became progressively worse and on the third day she presented mild dehydration and blood eosinophilia. After OIT interruption, a progressive clinical improvement was observed. An esophageal endoscopy was performed, showing signs of eosinophilic esophagitis (EoE) with peak 20 eosinophils/hpf. After treatment with topical swallowed fluticasone (500 mcg bid) and a CM-free diet for 4 months, the child was asymptomatic and endoscopy and biopsy findings were normal.
The long-term effects of milk OIT are still in part unknown. We hypothesize that eosinophilic esophagitis may have been a consequence of OIT in this case. The findings seem to indicate that food allergy may play a role in the pathogenesis of esophageal eosinophilia and stress the importance of a well programmed long-term follow-up of patients that have undergone milk OIT.

Case Report

Cow's milk (CM) allergy is a common disorder for which the standard of care is strict food avoidance. In recent years, CM oral immunotherapy (OIT), achieved by oral exposure to increasing doses of the food, has received particular attention as an alternative in cases where spontaneous tolerance acquisition is unlikely (1), increasing both quality of life and safety in the event of accidental ingestion of the offending food. Immediate adverse reactions during OIT have often been reported and seem to occur in 50 to 100% of cases (2-5). Delayed reactions, however, are much less often reported (3,5).

We present the case of a 3-year old girl with atopic eczema and CM allergy. This condition manifested at 2 months of age in association with several episodes of urticaria, angioedema and vomiting following CM ingestion. IgE-mediated allergy was confirmed by skin prick tests, positive serum specific IgE (sIgE) and a positive oral food challenge. A complete eviction of CM from her diet resulted in resolution of all symptoms.

At the age of 3 years and 9 months, after several immediate reactions with cutaneous and gastrointestinal involvement associated with unintentional CM ingestion, and since sIgE levels were persistently elevated (milk: 60 KUA/L; casein: 29 KUA/L), the child was proposed to undergo a OIT protocol (6). Consent from our institution's review board and from her parents was obtained prior to protocol start.

It consisted of administration of increasing doses of CM in our outpatient allergy center at 2 to 3 week intervals followed by daily consumption of the tolerated dose at home. In the first session, a dose of 1 ml was reached and mild immediate reactions (facial urticaria, oral itching) were observed. No reactions occurred during the maintenance period at home, thus a new dose escalation was done from 1 to 5 ml after 3 weeks. Thereafter, parents were instructed to maintain a daily morning dose of 5 ml at home. On the following day however, the child developed vomiting episodes approximately eight hours after CM ingestion. No other symptoms, particularly immediately after the dose, were reported. These episodes became progressively worse and on the third day she returned to the hospital. She looked ill and mildly dehydrated. A complete blood cell count revealed 1020 eosinophils/mm^3 (prior levels were 340 eosinophils/mm^3). At this time point, OIT was interrupted and progressive clinical improvement was observed on the course of the following days. Five days later an esophageal endoscopy was performed, showing rings and white mucosal exudates with a peak of 20 eosinophils/hpf in mucosal biopsies from the upper, middle and lower esophagus. Gastric and duodenal biopsies had no alterations and *Helicobacter pylori* (HP) and *Giardia lamblia* were absent. Markers for celiac disease and HP were negative. A pH-monitoring test was attempted but not tolerated by the child. Subsequent skin tests with other foods commonly associated with eosinophilic esophagitis (EoE) were negative.

Treatment was started with lanzoprazol but there was an episode of vomiting and urticaria immediately after the first dose, and therefore a decision was made to initiate topical swallowed fluticasone therapy (500 mcg bid) immediately. After a 4 month treatment with fluticasone and a CM-free diet, the child was asymptomatic and a new endoscopy with multiple biopsies found no alterations. Fluticasone was stopped and CM avoidance was maintained until now. At present, the child remains symptom-free 28 months after fluticasone discontinuation. Control endoscopies and biopsies performed at 12 and 27 months showed no sign of esophagitis. Specific IgE measured 14 months after the interruption of OIT was slightly higher (milk: 70 KUA/L; casein: 41 KUA/L) and presently a spontaneous decrease is observed (milk: 34 KUA/L; casein: 27 KUA/L).

We describe a patient with a typical history of IgE-mediated CM allergy, who developed a different clinical profile after the beginning of OIT: initial immediate skin and gastrointestinal reactions associated with CM ingestion developed into late gastrointestinal symptoms at the third week of OIT protocol.

EoE is an immune-mediated disorder in which the esophagus is infiltrated by eosinophils, presumably through a TH_2-driven process (7). In this case, diagnosis was confirmed by endoscopy and biopsy findings. Recovery following withdrawal of CM suggests a probable causal relation with CM ingestion during OIT. As no endoscopy was performed prior to OIT, we can only speculate that EoE developed during the treatment. However, symptoms of recurrent vomiting and malaise were absent previously, and blood eosinophilia also developed only after initiation of the protocol. According to recent guidelines (7) proton-pump inhibitor therapy was attempted, in order to discard gastroesophageal reflux disease or proton-pump inhibitor-responsive esophageal eosinophilia. Unfortunately, it had to be interrupted due to an apparent adverse reaction and a decision was made not to delay swallowed fluticasone therapy. It was therefore not entirely possible to exclude those diseases. However, we consider that the fact that the child remained asymptomatic and free of histologic abnormalities long after interruption of pharmacological treatment, strongly supports the diagnosis of CM induced EoE.It has been hypothesized that exposure of the esophagus of predisposed individuals to high antigen loads may be the core mechanism responsible for the development of EoE (8). In animal models, mice with respiratory, oral or epicutaneous sensitization that are rechallenged with intranasal exposure to allergens, develop esophageal eosinophilic infiltrates which mimic EoE (9,10). In humans, cases of EoE have been attributed to large volume allergen exposures (8), aeroallergen sublingual immunotherapy (11) and OIT (12-14).

Our review has found reports of 4 patients who developed EoE following CM OIT protocols (12,13). Furthermore, OIT protocols with peanut (3) and egg (13,14) have also been implied. Although this condition is probably underdiagnosed, the scarcity of reports suggest that EoE associated with OIT is likely rare. This is the first suggestive case in over 30 CM OIT performed in our center.

Although a favorable outcome seems to have occurred in this case, long-term evolution of esophageal eosinophilia and EoE is still uncertain. We agree with authors (12) who suggest that in the presence of this reaction, OIT should be interrupted.

The long-term effects of CM OIT are still in part unknown and adverse reactions may be more common than previously expected. The findings in this case seem to indicate that food allergy may play a role in the pathogenesis of esophageal eosinophilia and possibly of EoE and stress the importance of a well programmed long-term follow-up of patients that have undergone CM OIT.

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An unusual complication of late onset allergic contact dermatitis to povidone iodine in Oral & Maxillofacial Surgery – A report of 2 cases

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Key Words

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Summary

Background. *Povidone iodine (PVP-I) is a chemical complex of polyvinylpyrrolidone (also known as povidone or PVP) and elemental iodine. Iodine containing compounds are widely and commonly used as antiseptics and disinfectants. They are available in various forms like aqueous solution, tincture, aerosol, ointment, or foam. Skin irritation to them is due to the oxidative effects of iodine. Because of the low free iodine concentration in povidone-iodine, skin irritation is less frequent from short contact (1).* ***Case.*** *We report two cases, both with no history of allergy to any drugs, who developed an allergic reaction 24 hours after the usage of povidone iodine as a pre-operative antiseptic to prepare (scrub) the lower third of face before surgical removal of third molars. This case report was granted an exemption by the ethical committee of our institution review board. The Helsinki declaration doesn't apply to this case presentation.* ***Conclusion.*** *PVP-1 is the most commonly used antiseptic scrubbing solution prior to most surgeries. However, allergic contact dermatitis due to PVP-I has not been extensively documented or reported and hence under evaluated, compared to other commonly encountered allergens. There is almost general agreement to the proposition that PVP-I is a very rare sensitizer (2,3) though there are some conflicting reports on the matter. However, sometimes when prolonged skin contact with PVP-I occurs when used as a pre-operative antiseptic agent, it can cause allergic dermatitis (4,5). Does this finding make pre-operative testing for allergies to PVP-1 necessary in all patients? A point to ponder.*

Introduction

Povidone iodine preparations were introduced in the 1960s and are now the most common iodophor in clinical use because of their broad antimicrobial spectrum of activity, and unrivalled antiseptic properties. They are available in different formulations including solutions, creams, ointments, sprays and wound dressings. Povidone is a polymer similar to dextran and it acts as a carrier that delivers complexed diatomic iodine, which is bactericidal. It affects the structure and functions of enzymes and cell proteins. It also damages bacterial cell function by blocking hydrogen bonding and altering the membrane structure. These multiple modes of action ensure the rapid death of microbes, and also importantly help to prevent the development of bacterial resistance (6). Acute or late onset allergic contact or irritant dermatitis due to povidone-iodine is a rare complication, especially keeping in mind the extensive usage of the same. Systemic reactions to povidone-iodine are rare, but there are case reports of generalised urticaria and even anaphylactic shock (7,8). These cases have the characteristics of IgE-mediated reactions and in one case specific IgE against povidone was found.

Cases

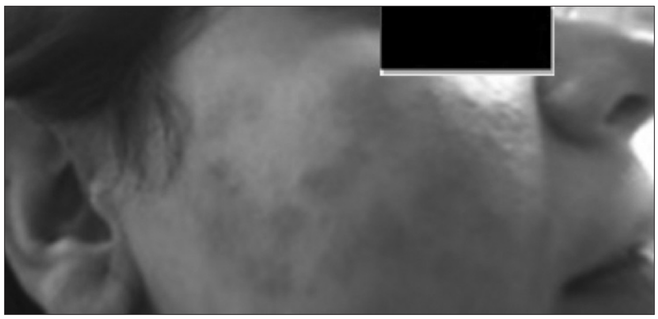
Two patients reported to the Department of Oral & Maxillofacial Surgery with a chief complaint of pain in lower back tooth region of jaw. A detailed case history of both the patients was recorded and it did not reveal any history of systemic disorders including asthma or allergy to any medication. Routine blood investigations were carried out, which were within normal limits. Preoperative orthopantomogram was ordered, which showed partially erupted lower third molars with inflamed pericoronal flap. Surgical removal of third molars was decided as a treatment plan for both the patients.

Patients were positioned on dental chair in semi-reclined position and face was first scrubbed with savlon. The savlon was then wiped using sterile gauze. The face was then painted with 5% povidone iodine solution and draped with a sterile cloth, as a part of the standard protocol followed preoperatively before surgical removal of third molars. The procedure in both cases was carried out as planned (based on the evidence provided by the orthopantomogram regarding the position of the offending tooth) without any unforeseen complication. The average duration for the procedure was approximately 45 minutes. Standard post-operative antibiotics and analgesics (Amoxicillin 500 milligrams and Diclofenac sodium 50 mg, paracetamol 325 mg) were prescribed. Both the patients were not given pre-operative or post-operative IV steroid because, as per the evidence provided by the orthopatomogram, excessive bone guttering or soft tissue retraction wasn't needed during the procedure.

Both the patients reported 24 hrs after the procedure with complaint of rashes only over the face, in the region painted with the PVP1 solution prior to the surgical removal. The patient first noted a stinging or burning sensation, with the onset of erythematous plaques that spread on both sides of the face over cheek region. On further clinical examination, a diffuse erythematous patch over the face, which was slightly oedematous with follicular elevations looking like tiny papules, were observed in both the patients. The erythematous patches were confined only to the areas which were painted with 5% povidone iodine. Although intra-oral irrigation was done using the same solution (a diluted solution 1:10 with normal saline) there were no inflammatory or allergic reactions seen intra-orally. Both the patients were referred to a dermatologist, and the diagnosis arrived at in both the instances was contact allergic dermatitis due to povidone iodine, for which both the patients were advised to use a desquamating soap; topical and systemic steroids as well as systemic antihistamines were prescribed (Systemic antihistamines Tab Cetrizine 10 mg bid, Tab Dazit 5 mg once daily, Inj Dexona 4 mg and vitamin E ointment (Evion cream) for local application). Both the patients were advised to avoid exposure to sunlight to prevent aggravation of the symptoms. With this treatment protocol, case 1 took 10 days to show complete regression of the symptoms, whereas only 1 week was sufficient for the symptoms to subside in case 2.

Figure 1 - *Case 1.*

Figure 2 - *Case 2.*



Discussion

Povidone-iodine 5% is a compound of iodine (0.5% releasable iodine but only 0.001% free iodine) and povidone, with additives of glycerin, nonoxynol-9, disodiumphosphate, citric acid, and polyoxyethylene nonylphenyl ether. It is commonly used as an antibacterial agent and antiseptic. Povidone itself is also used in products such as foods, medicaments, hair cosmetics, and toothpastes (9). Povidone is a synthetic polymer used as a suspending agent for many pharmaceutical products, including iodine. In this form, povidone-iodine is a commonly used antiseptic in a variety of surgical cases, providing a broad spectrum of germicidal properties against a wide range of bacteria, viruses, fungi, protozoa, and spores. Systemic absorption after topical application can potentially lead to immunoglobulin E (IgE) mediated allergic reactions. In its most benign form, local skin pruritus and irritation occur and resolve shortly after removal of povidone-iodine from skin (10). More severe reactions to povidone-iodine leading to anaphylaxis have also been seen in patients with an allergy to components of povidone-iodine. Less commonly reported are cases of angioedema immediately after contact with povidone-iodine (11). Regardless of the severity of symptoms, most reported reactions have developed immediately after exposure to povidone-iodine, representing the early phase of an IgE-mediated allergic reaction. Fewer cases of late phase allergic reactions have been reported with symptoms presenting 6-8 hours after exposure (12). Unique in our cases were that our patient did not have any history of allergic reaction and exhibited no immediate signs of a reaction after exposure to the agent. Their symptoms became apparent almost 24 hours after exposure to povidone-iodine. This is the most commonly used antiseptic scrubbing solution used prior to surgeries. Every clinician should be aware of the potential allergic reaction that the solution may cause (and in some cases due to prolonged exposure). Most clinical setups have a protocol to test for safety of the local anesthetic solution for a particular patient by giving the so called ‘test dose’ subcutaneously prior to the procedure. The question is whether reports of allergic reaction to PVP1 solution warrant a similar pre-operative testing protocol, to avoid such complications.

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