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For example:

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Perceived efficacy and satisfaction of patients with subcutaneous hypoallergenic high-dose house dust mite extract

Introduction

The efficacy and safety of subcutaneously administered allergen-specific immunotherapy (AIT) is widely supported by numerous meta-analyses published on both the treatment of bronchial asthma (1-4) and IgE-mediated rhinitis (5). The preventive effect on the natural course of the allergy in patients with rhinitis should also be noted (6-8). Patient compliance, appropriate patient selection for treatment with AIT and the most appropriate therapeutic extract are vital factors in achieving the desired therapeutic objectives in the event of prolonged treatment over time, as the recommended duration is no less than 3 years (8).

Therefore, given the increasingly active role of patients as health service users (9), it is important that both their perception of efficacy and their expectations, which are based on the information given by the prescriber, are taken into consideration to ensure that satisfaction with the various aspects of their treatment is as high as possible, thereby promoting appropriate adherence to treatment and compliance.

The optimum treatment to maximise patient adherence to treatment should involve the patient’s knowledge and expectation regarding the time from treatment initiation to symptom relief, the degree of improvement to be achieved, rapid and evident efficacy, a treatment regimen that is as easy and short as possible and minimal side effects. Patient time and travel are
also two additional factors related to patient-initiated treatment discontinuation (10,11).

Reducing the allergenicity of allergen extracts through chemical modification with aldehydes without affecting their immunogenicity allows physicians to administer a maintenance dose of major allergens at the upper end of the WHO-recommended scale for the most effective results (9).

Double-blind, placebo-controlled studies have shown (12-14) that subcutaneous immunotherapy with modified, high-dose, major allergen house dust mite extract is safe and effective. However, no data is yet available on patient-perceived efficacy and satisfaction with the treatment. Therefore, the objective of this study was to evaluate these aspects in the first year of treatment in the context of the normal clinical practice of the researchers involved.

Methods

Allergen extract composition

Acaroid® (Allergopharma GmbH & Co. KG, Reinbek, Germany), the product tested, is an aluminium hydroxide-adsorbed depot allergoid preparation of standardised high concentrations of powdered diafiltered dust mite allergens modified with formaldehyde and glutaraldehyde. There are two different concentrations: strength A (1,000 TU/ml) and strength B (10,000 TU/ml). The manufacturer-recommended maintenance dose is 0.6 ml of strength B (6,000 TU). Allergens quantified in the final step prior to allergoidisation are 11.66 μg/ml Der p 1, and 10 μg/ml Der p 2 in the 100% Dermatophagoides pteronyssinus formulation, and 20 μg/ml Der f 1 and 15 μg/ml Der f 2 in the 100% Dermatophagoides farinae formulation.

Study design

An observational, retrospective, multicentre, nationwide study was conducted with 47 investigators from 8 autonomous regions. The study was approved by the ethics committees of the participating hospitals and the Spanish Agency of Medicines and Medical Devices (AEMPS) was notified. During the observational period, investigators collected data from patients who met the following study inclusion criteria: 5-65 years of age with IgE-mediated rhinitis and/or bronchial asthma caused by house dust mites who had been considered for Acaroid® treatment as part of normal clinical practice and who were seen for follow-up within the first year of treatment for a minimum of 6 months.

To evaluate perceived efficacy, patients assessed their condition on a Visual Analogue Scale of 1 (worst) to 100 (best). Relevant clinical improvement was defined as an increase of at least 20 points compared to the self-assessed score before commencing treatment and at the time of the evaluation (1,15).

A questionnaire including a series of questions grouped into a number of variables was used to determine the degree of satisfaction of patients treated with Acaroid®. The variables included in the questionnaire were: the need for treatment to be administered subcutaneously and for this to be done by a healthcare professional, the impact having to go to the health centre had on subjects’ daily routine, the level of improvement in symptoms with treatment and overall satisfaction with treatment. A Likert scale was used to objectively evaluate the questionnaire’s variables, with 5 representing most satisfied (16).

Statistical analysis

The estimated sample size was calculated on the basis of the number of investigators involved. As this was an observational, retrospective study, which depended on the feasible number of patients for whom each investigator may consider administration of Acaroid® appropriate in their usual clinical practice, it was not possible for the optimal sample size to be calculated in advance.

A descriptive analysis of all the variables in the patient questionnaire was carried out for the entire sample. Mean and standard deviation (SD) in normally distributed variables were used as statistical descriptions of quantitative variables, and median and interquartile range if distribution was not normal. For the categorical variables, proportions were used. In the bivariate analyses, average-to-average for normally distributed continuous variables and nonparametric tests for non-normal distribution were used. A contingency analysis for categorical variables was carried out. The significance level of the statistics calculated was p < 0.05.

Results

Between September and November 2012, data was collected from patients diagnosed with dust mite IgE-mediated rhinitis and/or bronchial asthma who had commenced treatment with Acaroid®. A total of 435 patients were recruited, of whom 130 (29.9%) were paediatric. 420 patients (96.5%) had a diagnosis of rhinitis and 236 (54.2%) had bronchial asthma (table 1).

Patient-perceived efficacy

The patients’ overall score increased by 33.8 points (from 42.6 to 76.4 points; p < 0.001, giving a perceived efficacy of 79.34%), an improvement of between 30 to 50 points for 50.5% of the overall population (220 patients), which was clinically significant (> 20 improvement points) in 362 patients (83.2%). In the paediatric population, the overall improvement was 35.3
points (42.3 to 77.6 points, p < 0.001, giving a patient-perceived improvement of 83.45%), with an improvement of between 30 to 60 points for 54.61% of the population and over 20% (clinically significant) in 108 patients (83.07% of the total) (figure 1 and 2).

**Table 1 - Population demographics.**

<table>
<thead>
<tr>
<th></th>
<th>Overall population</th>
<th>Paediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>435 (100%)</td>
<td>130 (30%)</td>
</tr>
<tr>
<td>Age Range</td>
<td>5-65</td>
<td>5-16</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>24.6 (13)</td>
<td>10.9 (3)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>204 (46.9%)</td>
<td>88 (67.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>231 (53.1%)</td>
<td>42 (32.3%)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis / rhinoconjunctivitis</td>
<td>420 (96.5%)</td>
<td>123 (94.6%)</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>236 (54.2%)</td>
<td>77 (60.2%)</td>
</tr>
<tr>
<td>Acaroid® composition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>House dust mite mix</td>
<td>262 (60.2%)</td>
<td>87 (68%)</td>
</tr>
<tr>
<td>D. pteronyssinus</td>
<td>172 (39.6%)</td>
<td>41 (32%)</td>
</tr>
<tr>
<td>D. farinae</td>
<td>1 (0.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Interpreting the graph: the bars represent the individual improvement for each patient group and the two vertical lines represent the mean pre-treatment and post-treatment score (standard deviation), 42.6 and 76.4 respectively (p < 0.001).

**Satisfaction questionnaire**

Overall patient-satisfaction with the treatment was 4 (out of a maximum of 5 points), with 224 patients being very satisfied (51.5% of the population). No differences were observed in the paediatric sub-population.

The need for treatment to be administered by a healthcare professional was well received by 95.1% (414 patients), which was consistent with the results obtained for the impact having to go to a medical centre for administration had on the subject's daily routine, which was not a drawback for 86.8% (375 subjects).

Although subcutaneous administration was not a significant drawback for 358 patients (82.3%), it was the variable with the lowest satisfaction score.

When study subjects were asked if the treatment had resulted in a potential improvement in their symptoms, 324 of them (75% of total population) reported a clear clinical improvement (table 2).

The treatment was well tolerated by 429 patients (98.63% of the population). Six patients overall suspended treatment due to adverse events (1.37%).

**Figure 1 - Overall population satisfaction, mean score pre IT / post IT (SD).**
Perceived efficacy and satisfaction of patients with subcutaneous hypoallergenic high-dose house dust mite extract

During this study, no serological tests were performed or specific medication or symptom scores collected, as both the efficacy and safety of Acaroid® for rhinitis and/or IgE-mediated bronchial asthma caused by hypersensitivity to house dust mites had already been demonstrated previously in double-blind placebo-controlled studies (12-14).

We are aware of the limitations of the retrospective, observational design. However, we would also like to point out that as our intention is to evaluate patient opinion in routine clinical practice, we believe that the study design is conducive to the aforementioned objective.

In this sense, given the importance that patient-perceived efficacy and treatment satisfaction have in achieving adequate patient compliance, we believe that good data on efficacy may provide clinicians with a useful tool for achieving patient compliance in their daily practice. It may be useful not only in terms of short-term efficacy, but also for the ultimate objective of achieving sustained, long-term efficacy and changing the natural course of the allergy.

Reisacher et al. reviewed the literature on patient adherence to allergen-specific immunotherapy for allergic disease. They concluded that effective communication between the patient and...
the physician, and the simplicity of the regimen were frequently noted to be of primary importance (17). There is a need to further investigate potential barriers and measures to enhance persistence and compliance in order to increase desired clinical benefits from immunotherapy and reduce overall costs associated with discontinuation (17,18).

One of the drawbacks most commonly associated with subcutaneously-administered specific allergen immunotherapy is having to periodically visit a healthcare professional for administration, and the subsequent impact this has on the patient’s daily routine (10). The results obtained lead us to believe that this should not create a barrier to treatment but that the contrary is in fact true: knowing that each visit to the healthcare professional for administration allows them to control the course of their treatment and their health in terms of their allergy could encourage compliance and treatment-adherence, due to the safety and peace of mind it gives each patient. On top of this, delivery and treatment costs could be positioned as barriers for treatment adherence. However, results from a recent study do not appear to detect significant differences in adherence according to delivery route. Further research is required to enable any firm conclusions (11). As for treatment costs, the financial burden of SCIT is an important factor in patients discontinuing treatment (19).

These results are consistent with those presented by Pajno et al. (20) in a 3-year follow-up of a group of 2,692 patients, of whom 1,886 received subcutaneous immunotherapy and the rest, sublingually. It was seen that treatment-adherence was greater when administering subcutaneously versus sublingually. Although the worst aspect for patients, as is to be expected, is the fact that treatment is administered subcutaneously, the results demonstrate that when patients’ expectations in terms of efficacy and tolerability are met, this route of administration does not negatively affect target treatment compliance.

The high degree of tolerance obtained by the treatment, observed in 98.63% of patients, confirms the safety data demonstrated in earlier studies using this same therapeutic extract (12-14,21). Although the study objective was not to compare data on perceived efficacy and satisfaction in adult and paediatric patients, we consider that a paediatric sub-population of 29.9% of the total population (130 patients) merited particular reference to the results of this subpopulation.

The degree of satisfaction is positively correlated to improvement in patient-perceived symptoms and the administration of treatment by a healthcare professional. Matricardi et al. (22) recently published a comparative review of several meta-analyses in which they included at least 5 randomised, double-blind, placebo-controlled studies with the aim of evaluating the short-term efficacy of both symptomatic and allergen-specific medication. They concluded that, in the first pollen-season following commencement of immunotherapy, based on the nasal symptom score, allergen-specific immunotherapy was at least as effective as the symptomatic treatment available for patients with allergic rhinitis.

Conclusion & future perspective

In long-lasting treatments, two key factors for a successful outcome are patient compliance, and in relation, good patient satisfaction and patient-perceived effectiveness in the early stages of the treatment. The results obtained in this study demonstrate how subcutaneous immunotherapy with high-dose modified house dust mite allergens is effective and well tolerated in an allergist’s daily practice. The patients’ condition demonstrated a clear and marked improvement in the first 6 months following commencement of treatment. Overall, patient satisfaction with Acaroid® treatment is in the range of very satisfied. The patients’ overall perceived efficacy score increased by 33.8 points and 35.3 for the overall and paediatric population respectively.

The results shown here indicate a very good perspective in terms of efficacy and patient perception in the treatment of allergies. It is really remarkable that after 6 months of treatment the patient perceives an improvement of symptoms, which promotes greater adherence to treatment, with better prospects for treatment and preventing relapse. Further studies with a special focus on patient adherence and therapeutic compliance, with a longer follow-up, and linking the perceived short-term efficacy in routine clinical practice are needed.

Conflict of interest

Merck’s Medical Affairs Department, represented by N. Cancelliere and J. Álvarez Nieto, has been actively involved in the elaboration of the manuscript. However, this collaboration has not influenced at any point the data presented in the study.

References

M. Gelardi¹, R. Guarino¹, S. Taliente¹, N. Quaranta¹, A. Carpentieri¹, G. Passalacqua²

Allergic and nonallergic rhinitis and skin sensitization to metals: is there a link?

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²Allergy and Respiratory Diseases, IRCCS San Martino-Ist-University of Genoa, Genoa, Italy

Key words
Allergic rhinitis; non-allergic rhinitis; Contact dermatitis; Chromium; Cobalt; Nickel; inflammation

Summary
Background. Chromium, Cobalt and Nickel are responsible for contact dermatitis, that is largely prevalent in the general population. They can act also as irritants in the upper and lower respiratory airways. Also rhinitis (allergic and nonallergic) is a high prevalence disorder. Both diseases could share some common inflammatory mechanisms, but the clinical association between skin sensitization to metals and rhinitis was never studied. Objective. We assessed the presence of skin sensitization to metals in subjects with rhinitis. Methods. Patients suffering from rhinitis underwent a standard diagnostic procedure, including skin testing, nasal endoscopy and nasal cytology. Control healthy subjects were also included. None of the patients had skin diseases. All subjects underwent patch test with Chromium, Cobalt and Nickel. Results. None of the 26 controls had positive skin prick test or nasal cytology. The 82 rhinitis patients were subdivided into allergic (group A = 27), nonallergic (group B = 31) and overlapping (group C = 24). The prevalence of positive patch test to metals was 26% in group A, 45% in group B, 42% in group C and 31% in controls. The percentage of patch-positive subjects was significantly different between Group A and B (p = 0.0045; OR: 0.43), Group A and C (p = 0.0186; OR: 0.49), and Group B and controls (p = 0.0360; OR: 1.85). There was a significant difference between groups A + controls and B + C. Conclusion. Even in the absence of skin diseases, the prevalence of sensitization to metals (patch test) is greater in nonallergic and overlapping rhinitis, as compared to allergic rhinitis and controls.

Introduction
Chromium (Cr), Cobalt (Co), Nickel (Ni) and their salts are the metals most frequently responsible for contact dermatitis (CD). The trivial definition of contact “allergic” dermatitis mainly relies on historical bases, but the mechanisms of CD are not IgE-mediated, and rather involve a delayed T-cell inflammation. In Europe, the prevalence of CD due to Ni, Co and Cr is estimated around 20%, 7% and 4%, respectively. Of note, Italy seems to have the higher prevalence of CD (around 32%) (1), similar to that reported in the USA (2,3). The occurrence of CD is most frequent in women, since Ni and Co are largely used in jewellery and cosmetic products (4). On the other hand, Cr-related CD is observed more frequently in men, due to occupational exposure (5). Such metals can act also on the respiratory mucosae, especially in the nose, where they can induce an irritative or vasomotor rhinitis (6). As a matter of fact, both rhinitis and CD are high prevalence diseases and share an inflammation-driven mechanism (mainly Th2 and IgE-mediated in allergic rhinitis, cell-mediated in CD and largely unknown in nonallergic rhinitis). Nonetheless, nothing is known about the possible relationship between rhinitis (either allergic or nonallergic) and skin
sensitization to metals. Thus, we attempted to evaluate if some relationship exists between these two diseases (CD and rhinitis), based on clinical and biological observations.

Methods

Consecutive adult and adolescent subjects, referred to our Unit for rhinitis symptoms between October 2014 and April 2015, were evaluated. The patients underwent a standard diagnostic work-up, including allergy diagnosis, nasal endoscopy and nasal cytology. In addition, all of them underwent a patch test procedure to assess the presence of skin sensitisation to Ni, Co and Cr. Patients with mechanical / anatomical nasal abnormalities (polyposis, rhinosinusitis, turbinate hypertrophy) were not included. According to the clinical and biological characteristics of rhinitis, patients were subdivided into 3 groups: A = allergic rhinitis (at least one skin prick test, SPT, positive); B = non-allergic rhinitis (nasal inflammation with negative SPT); C = overlapping rhinitis (positive SPT and discordant nasal cellular profile). A group of healthy subjects, without nasal symptoms and with negative tests was also included. None of the enrolled subjects had clinical or historical evidence of skin diseases. All patients (or their legal caregiver) provided an informed consent. The study was approved by Inner Ethical Committee of Bari University.

Clinical evaluation. After collecting the personal data into a dedicated database, all subjects underwent a detailed clinical history, including family history, duration of symptoms, seasonality, comorbidities (e.g. asthma, polyposis, systemic diseases, malignancies) according to guidelines (7). An external inspection of the nose and conjunctiva was carried out to exclude gross abnormalities, and a general clinical visit was performed, where vital parameters were recorded.

Nasal endoscopy. It was carried out with a 3.4 mm diameter flexible nasal endoscope (Vision-Sciences® ENT-2000), to assess the presence of major abnormalities, such as septal deviation, polyposis, turbinate hypertrophy, or exudation from the ostiomeatal complex.

Nasal cytology. This procedure was performed by scraping the middle part of the inferior turbinate with a Rhino-Probe® device (Arlington Scientific). The sample was smeared on a slide, air-dried, then stained with the May-Grünwald Giemsa preparation. Type and cell number were examined using microscopy (Nikon® E600). Cell types were identified, and intracellular components were studied at x 1000 in oil immersion. The mean number per 50 fields was calculated and reported (8,9).

Skin prick test. It was performed and read according to the recommendations of the European Academy of Allergy and Clinical Immunology (10). A standard panel with the most common aeroallergens (Stallergenes, Milan, Italy) was used: house dust mite, grass mix, parietaria, olive, cypress, compositae mix, alternaria, ragweed, cat and dog dander.

Patch test. It was performed according to guidelines of the European Society of Contact Dermatitis. Four substances were applied to assess the presence of skin sensitisation to Ni, Co and Cr. Thus, we attempted to evaluate if some relationship exists between these two diseases (CD and rhinitis), based on clinical and biological observations.

Table 1 - Demographic, clinical and cytological characteristics of the studied population.

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 27)</th>
<th>Group B (n = 31)</th>
<th>Group C (n = 24)</th>
<th>Group D (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>35.1</td>
<td>47</td>
<td>35.5</td>
<td>41.1</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>16-67</td>
<td>23-80</td>
<td>15-68</td>
<td>17-66</td>
</tr>
<tr>
<td>M/F</td>
<td>12/15</td>
<td>13/18</td>
<td>10/14</td>
<td>5/21</td>
</tr>
<tr>
<td>Moderate / severe rhinitis</td>
<td>25/27</td>
<td>31/31</td>
<td>22/24</td>
<td>0</td>
</tr>
<tr>
<td>2 or more positive skin test, N</td>
<td>22</td>
<td>0</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Monosensitized, N (%)</td>
<td>5 (19)</td>
<td>0</td>
<td>12 (54)</td>
<td>0</td>
</tr>
<tr>
<td>Nasal cytology1</td>
<td>Neutrophils</td>
<td>10.4 (33.8)</td>
<td>20.6 (41)</td>
<td>22.4 (49.7)</td>
</tr>
<tr>
<td></td>
<td>Eosinophils</td>
<td>4.2 (8.8)</td>
<td>9.7 (11.6)</td>
<td>11.3 (11.5)</td>
</tr>
<tr>
<td></td>
<td>Lymphocytes</td>
<td>0.3 (1.5)</td>
<td>0.6 (3.7)</td>
<td>0.7 (2.3)</td>
</tr>
<tr>
<td></td>
<td>Mast cell</td>
<td>1.1 (4.2)</td>
<td>5.3 (11.4)</td>
<td>6.5 (7.5)</td>
</tr>
<tr>
<td>Any patch test positive</td>
<td>7 (26%)</td>
<td>14 (45%)</td>
<td>10 (42%)</td>
<td>8 (31%)</td>
</tr>
<tr>
<td>Ni</td>
<td>5</td>
<td>12</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Co</td>
<td>4</td>
<td>4</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Cr</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

1Mean cell count on 50 fields (SD)
plied: Nickel sulphate esahydrate 5%, Cobalt II sulphate 2.5%, Chromium sulphate 0.5% and white petrolatum as negative control. The results were read 48 hours after the application of the test (11).

Statistical analysis. The Chi-square test was applied to the parameters considered, to identify the differences among groups.

Results

Eighty-two patients (35 male, mean age 41 years, age range 15-80 years), were studied at our Unit between October 2014 and April 2015. All of them suffered from rhinitis symptoms (moderate / severe in 78/82), whereas the healthy control group included 26 patients (5 male, mean age 41 years, age range 17-66 years). No difference in the severity of the disease could be detected among groups. The demographic and clinical characteristics are summarized in table 1.

According to the results of the diagnostic work-up, 27 patients (32.9%) had allergic rhinitis (Group A) (5 monosensitized), 31 (37.8%) had non-allergic rhinitis (Group B) with various cytological profiles: 17 non-allergic rhinitis with eosinophils (NARES); 4 non-allergic rhinitis with mast cells (NARMA); 10 non-allergic rhinitis with eosinophils and mast cells (NARESMA) (12-14). Finally, 24 patients (29.3%) had an overlapping rhinitis (group C), that is with allergic sensitizations and a cellular profile typical of vasomotor rhinitis (Group C): 7 NARES, 4 NARMA and 13 NARESMA (15). Obviously, all the 26 patients in the control group (Group D), had no symptoms of rhinitis, negative skin test and negative nasal cytology.

A patch test positivity (to one or more of the tested metals) was found in 7/27 patients in group A, in 14/31 in group B, in 10/24 in group C and in 8/26 in the control group. A significant difference in the percentage of patch-positive subjects was found between Group A and B (p = 0.0045; OR: 0.43), Group A and C (p = 0.0186; OR: 0.49), and Group B and D (p = 0.0360; OR: 1.85) (Figure 1). Also, there was a significant difference between groups A + D and B + C (p = 0.0239; OR: 1.96).

Discussion

Some metals are largely present in our life, as components of foods and beverages (e.g. canned meat, vegetables or shellfish), or used in jewellery, or in various occupational fields. In fact, Ni is responsible for a number of cases of CD, greater than those caused by all other metals, as testified by the abundant literature. The occurrence of CD is increasing in adolescents, probably in relation to the use of metal-containing devices or ornaments (16). Despite often including the term “allergic”, CD is not IgE-mediated, but a type 4 cell-mediated immunological disease. It appears as an eczema (primary eruption) that is well confined to the skin areas which are in contact with the metal containing objects: ear lobes (earrings), wrists (bracelets), neck (chains), umbilical region (buttons). Metal allergy may also be present in systemic forms (secondary eruptions) that appear at sites different from those that are in contact with the metal (17) or, at least for Ni, with extra-cutaneous systemic manifestations, such as the Systemic Nickel Allergy Syndrome, with respiratory symptoms (18,19). In addition, some investigators suggested the possibility of a toxic effect on respiratory mucosae following a prolonged exposure: respiratory mucositis, vasomotor rhinitis, occupational asthma (20-25). Of note, an increased rate of sensitisation to metals was previously reported in asthmatic patients (26). Nonetheless, there is scarce information on the possible relationship between non-occupational exposure to Ni, Cr or Co and respiratory diseases, although it is conceivable that the pathophysiological mechanism are in part similar, due to the involvement of the adaptive arm of immunitary response, as demonstrated in asthma (27). The use of nasal cytology allows to better distinguish the “vasomotor” rhinitis, characterized by an intense cellular infiltration (NARES, NARMA, NARESMA), from the classic allergic rhinitis and from the overlapping forms (28).

According to the results of our study, it seems that the cutaneous sensitization to metals is less frequent in patients with allergic rhinitis, and more prevalent in those with non-allergic rhinitis or overlapping disease (as confirmed by the sums of group A+D and C+D). Indeed, we could not provide a pathophysiological explanation, and simply we described a phenomenon, that was
not investigated before. Nonetheless, it is conceivable that the association of metal sensitisation and nonallergic rhinitis is not simply “by chance”, and would deserve further investigations.

References


Summary

Rationale. Recent data suggest that the nutritional status assessed by body mass index (BMI) is positively associated with skin reactivity to histamine in children. Objective. To study the relation between BMI and skin reactivity to histamine and Dermatophagoides pteronyssinus in allergic children and adolescents. Methods. The medical charts of patients attended in our outpatient clinic between 2013 and 2014 (n = 972) were evaluated. Only patients with asthma, allergic rhinitis or wheezing infants sensitized to at least one aeroallergen were selected: a total of 626 patients (6 months to 19 year-olds; 60.1% male) were enrolled. Weight (kg), height (m), BMI (weight/height$^2$), and the mean diameter of the wheals induced by histamine (10 mg/ml) and Dermatophagoides pteronyssinus in skin prick tests (SPT) were obtained. Skin index (SI; ratio of allergen-induced wheal diameter and corresponding histamine diameter) was also analyzed. Results. All patients had shown a mean wheal diameter of histamine greater than 1 mm. There was no increased skin reactivity to histamine with increasing BMI Z score (ZBMI). However, a significant correlation between BMI and the mean wheal of histamine was observed in patients < -1 ZBMI. Similar results were observed with Dermatophagoides pteronyssinus, (even considering the SI). Conclusions. We did not document interference of nutritional status (ZBMI) on the skin reactivity to histamine or Dermatophagoides pteronyssinus in atopic patients. Further investigation is required.

Key words

Allergic sensitization; histamine; skin index; skin prick tests; body mass index

Introduction

Skin prick test (SPT) is an important tool in the assessment of allergic sensitization and can be influenced by various factors: age, ethnicity, body site where the test is performed (1,2), exposure to smoking (3), use of certain drugs, type of devices used, etc. (1,2).

Association between asthma and/or allergic rhinitis with obesity is becoming more common. Considering that both diseases are associated with systemic inflammation (4), obesity could interfere with in vivo evaluation of allergic sensitization. Recently, the nutritional status assessed by body mass index (BMI) was documented to be associated in children (5) and adults (6) with increased skin reactivity to histamine. Although both studies evaluated histamine skin response in allergic patients, in none of them was analyzed the relationship between BMI and skin response to individual allergen (5,6).

Therefore, the scope of this study was to evaluate the relationship between BMI and the mean diameter of the wheal induced by histamine and Dermatophagoides pteronyssinus (Dp) in children and adolescents treated at an allergy service.

Materials and Methods

Demographic (gender, age, diagnosis, prescription) and clinical data (weight [kg], height [m]) from patients aged 6 months to
19 years admitted in our division (2013-14) due to wheezing episodes, asthma, allergic rhinitis and food/drug allergy, were obtained from the electronic medical records (n = 972).

The subjects underwent SPT (puncture) with standard battery of allergens, used routinely in our service, composed by: Dp, *Dermatophagoides farinae*, *Blomia tropicalis*, *Blattella germanica*, *Periplaneta americana*, dog dander, cat dander, fungi mixture, milk, egg, saline (negative control), and histamine (10 mg/mL, positive control) (IPI ASAC®, Brazil) (7). SPT were performed by trained personnel using metal lancet. Antihistamines were interrupted at least 10 days before SPT. Patients with both positive SPT to at least one aeroallergen (mean wheal equal to or greater than 3 mm) (8) and with a mean histamine-induced wheal diameter equal to or greater than 1 mm were included in the study (n = 626) (figure 1). Patients with negative results to histamine or with positive response to negative control were excluded from the study (1,2).

A total of 626 children (60.1% males) were enrolled and 356 had positive skin test result to Dp. The children's nutritional status was evaluated by body mass index (BMI, weight / height², Anthro OMS.22 Plus®), compared to the World Health Organization (WHO) reference, and expressed in BMI Z score (ZBMI) (9). For analysis purposes, the data referring to histamine- and Dp-induced mean wheal diameter were evaluated by the Spearman's correlation coefficient. In all tests the rejection level for the null hypothesis was set at 5%.

### Results

During 2013-2014, 972 patients were admitted in our division, of which 87.2% had asthma and/or allergic rhinitis or were allergic to food/drug allergy, were obtained from the electronic medical records (n = 972).

The subjects underwent SPT (puncture) with standard battery of allergens, used routinely in our service, composed by: Dp, *Dermatophagoides farinae*, *Blomia tropicalis*, *Blattella germanica*, *Periplaneta americana*, dog dander, cat dander, fungi mixture, milk, egg, saline (negative control), and histamine (10 mg/mL, positive control) (IPI ASAC®, Brazil) (7). SPT were performed by trained personnel using metal lancet. Antihistamines were interrupted at least 10 days before SPT. Patients with both positive SPT to at least one aeroallergen (mean wheal equal to or greater than 3 mm) (8) and with a mean histamine-induced wheal diameter equal to or greater than 1 mm were included in the study (n = 626) (figure 1). Patients with negative results to histamine or with positive response to negative control were excluded from the study (1,2).

A total of 626 children (60.1% males) were enrolled and 356 had positive skin test result to Dp. The children's nutritional status was evaluated by body mass index (BMI, weight / height², Anthro OMS.22 Plus®), compared to the World Health Organization (WHO) reference, and expressed in BMI Z score (ZBMI) (9). For analysis purposes, the data referring to histamine- and Dp-induced mean wheal diameter were evaluated by the Spearman's correlation coefficient. In all tests the rejection level for the null hypothesis was set at 5%.

### Table 1 - Histamine-induced mean wheal diameter (M ± SD) and Spearman's correlation coefficients (r) between nutritional status (BMI Z score) and histamine-induced mean wheal diameter of patients according to age range and interval of BMI Z scores.

<table>
<thead>
<tr>
<th>BMI Z score</th>
<th>0 to 2 yrs</th>
<th>2 to 5 yrs</th>
<th>5 to 10 yrs</th>
<th>&gt; 10 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Histamine (95% CI)</td>
<td>r (95% CI)</td>
<td>N</td>
<td>Histamine (95% CI)</td>
</tr>
<tr>
<td>&lt; -1 a)</td>
<td>11 (3.86-5.60)</td>
<td>0.41</td>
<td>16 (4.19-5.22)</td>
<td>-0.24</td>
</tr>
<tr>
<td>-1 a +1 b)</td>
<td>36 (4.05-5.23)</td>
<td>-0.13</td>
<td>109 (4.48-5.15)</td>
<td>-0.36-0.01</td>
</tr>
<tr>
<td>+1 a +2 c)</td>
<td>20 (3.79-5.36)</td>
<td>0.52</td>
<td>43 (4.92-5.87)</td>
<td>0.04</td>
</tr>
<tr>
<td>&gt; +2 d)</td>
<td>10 (3.23-4.77)</td>
<td>0.16</td>
<td>26 (4.75-6.25)</td>
<td>0.03-0.70</td>
</tr>
</tbody>
</table>

BMI Z score: Body mass index Z score; 95% CI: 95% Confidence interval IC 95%; Kruskal-Wallis: Histamine: 0-2 yrs, 2-5 yrs, 5-10 yrs: a = b = c = d. Older than 10 yrs: a > b, c > d. Spearman’s correlation coefficient: ‘p < 0.05
wheezing infant, 73.9% were sensitized to at least one of the tested Aeroallergens (n = 626) and were included in the study, and 56.7% (n = 356) of them were sensitized to *Dermatophagoiodes pteronyssinus* (figure 1). BMI ranged from 10.9 to 37.8 and ZBMI from -4.7 to 6.3, with the following distribution: 2.7% patients below -2 ZBMI, 53.4% in the normal range (-1 to +1 ZBMI), and 15.5% were considered obese (> +2 ZBMI).

Table 1 shows the histamine-induced mean wheal diameter of patients according to age range and ZBMI score. No significant differences of histamine-induced wheal diameter between the different ZBMI intervals were observed with respect to each age range. Spearman’s correlation coefficient between histamine-induced mean wheal diameter and ZBMI was not significantly different, except for 2 to 5 years old age group and +1 to +2 ZBMI. Similar results were observed considering the Dp-induced mean wheal diameter (data not shown).

Table 2 summarizes the statistical analysis regardless of the age of the patients. In the whole group, there were no differences regarding age and mean histamine-induced wheal when considering the ZBMI groups; however, a significant correlation between ZBMI and histamine-induced wheal was observed among those subjects with BMI lower than -1 ZBMI (undernourished).

The evaluation of Dp-sensitized patients showed no significant differences with respect to the mean Dp-induced wheal. Nevertheless, a significant correlation was observed between ZBMI and Dp-induced wheal among those patients scored between +1 ZBMI and +2 ZBMI. Regarding SI (mean), there were no significant differences among ZBMI groups as well as no significant correlation between SI and ZBMI.

**Discussion**

When evaluating the skin response to histamine and/or allergens, it is important to be aware of when it is clinically present, which extracts and devices were applied, and the inter-individual variation in test run (1,2,9). Several studies have shown that, in the first month of life, the child’s skin is able to express an age-dependent inflammatory response to histamine (10-12). There were no differences regarding age among the different ZBMI groups assessed.

In addition, when evaluating skin response to histamine and allergen extracts, it is important to point out that the mechanism involved in each one is partially different. Histamine acts directly on the subcutaneous inflammatory cells causing local release of inflammatory substances, including histamine itself, while allergen extracts must penetrate the skin, bind to a specific Immunoglobulin E (IgE) fixed to the surface of mast cells, release inflammatory mediators that contain histamine, and present a clinical expression of the inflammatory reaction (wheat and

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**Table 2** - Age (M ± SD), histamine-induced mean wheal diameter (M ± SD), patients sensitized to Dermatophagoides pteronyssinus (+ve SPT / total, %), Dp-induced mean wheal diameter (M ± SD), skin index (M ± SD) and Spearman correlation coefficients (r) of the patients according to the nutritional status (ZBMI).

<table>
<thead>
<tr>
<th>ZBMI</th>
<th>N</th>
<th>Age (month) (95% CI)</th>
<th>Histamine M ± SD mm (95% CI)</th>
<th>r*</th>
<th>+ve SPT / Total (%)</th>
<th>Histamine M ± SD mm (95% CI)</th>
<th>r*</th>
<th>Dermatophagoides pteronyssinus M ± SD (95% CI)</th>
<th>r*</th>
<th>Skin index M ± SD (95% CI)</th>
<th>r*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>54</td>
<td>78.3 ± 58.7 (63.2-95.3)</td>
<td>5.5 ± 1.7 (5.0-6.0) (0.16-0.62)</td>
<td>0.42*</td>
<td>29/54</td>
<td>4.8 ± 2.1 (5.37) (4.0-5.6)</td>
<td>-0.12</td>
<td>0.84 ± 0.25 (0.75-0.94)</td>
<td>-0.37</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>-1 a +1</td>
<td>335</td>
<td>86.0 ± 55.7 (80.1-92.0)</td>
<td>5.3 ± 1.7 (5.1-5.5) (-0.05-0.16)</td>
<td>-0.06</td>
<td>197/335</td>
<td>5.0 ± 1.7 (58.8) (4.8-5.3)</td>
<td>-0.01</td>
<td>0.95 ± 0.36 (0.90-1.00)</td>
<td>-0.06</td>
<td>0.085</td>
<td></td>
</tr>
<tr>
<td>+1 a +2</td>
<td>140</td>
<td>84.2 ± 57.0 (74.8-93.7)</td>
<td>5.4 ± 1.7 (5.1-5.5) (-0.24-0.08)</td>
<td>-0.08</td>
<td>70/140</td>
<td>5.2 ± 2.3 (50.0) (4.7-5.8)</td>
<td>0.26*</td>
<td>0.97 ± 0.40 (0.88-1.10)</td>
<td>-0.08</td>
<td>0.166</td>
<td></td>
</tr>
<tr>
<td>&gt; +2</td>
<td>97</td>
<td>86.9 ± 47.9 (77.2-96.6)</td>
<td>5.8 ± 1.9 (5.4-6.2) (-0.01-0.38)</td>
<td>0.19</td>
<td>60/97</td>
<td>5.6 ± 2.1 (61.9) (5.0-6.1)</td>
<td>-0.23</td>
<td>0.036</td>
<td>-0.08</td>
<td>0.018</td>
<td></td>
</tr>
</tbody>
</table>

M ± SD: mean ± standard deviation; ZBMI: Z body mass index score; 95% CI: 95% confidence interval; +ve SPT: *D. pteronyssinus* positive skin prick test; skin index: ratio between mean wheal diameter induced by *D. pteronyssinus* and the corresponding histamine mean wheal.

**Histamine**

Kruskal-Wallis: age and mean wheal diameter, a = b = c = d;

r*: Spearman correlation index between ZBMI and histamine; *p < 0.05.

+ve SPT to *D. pteronyssinus*

Kruskal-Wallis: age, mean wheal diameter and skin index, a = b = c = d;

r*: Spearman correlation index between ZBMI and *D. pteronyssinus*; *p < 0.05.

r*: Spearman correlation index between ZBMI and skin index.
BMI and skin reactivity to histamine

References


2. Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG, Canonica GW, Carlsen KH, Cox L, Haagten L, Dølgaard HC. Sensitization to allergens in children treated in a specialized allergy service. Additional studies are needed to clarify this possible relationship more precisely.


The Vespid Allergy Quality of Life Questionnaire - cultural adaptation and translation to Portuguese

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³Allergy Unit, CUF-Porto Hospital and Institute, Porto, Portugal
⁴CINTESIS - Center for Research in Health Technologies and Information Systems, Porto, Portugal
⁵Immunology Lab / Clinical Pathology Department, Centro Hospitalar de São João E.P.E., Porto, Portugal
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Summary
A cross-cultural translation of the Vespid Allergy Quality of Life Questionnaire (VQLQ) to the Portuguese population (VQLQ-P) was performed, assessing its applicability in wasp and non-beekeeper bee venom allergic patients. Additionally, we evaluated a Visual Analogue Scale (VAS) to estimate hymenoptera allergy interference with daily life. Methods. Cross-cultural translation was performed according to recommendations. The final VQLQ-P version, the Expectation of Outcome questionnaire (EoQ), EQ-5D and VAS were applied to wasp (n = 19) and non-beekeeper bee venom allergic patients (n = 30). Results. VQLQ-P significantly correlated with EoQ, (r = 0.76, p < 0.01), EQ-5D (usual activities and anxiety / depression dimensions) and VAS, with a good internal consistency (Cronbach α = 0.88) in wasp allergic individuals. VQLQ-P and EoQ correlation was also high (r = 0.67, p < 0.01) in bee allergy. Conclusion. The VQLQ-P is a valuable tool to evaluate quality of life impairment in Portuguese hymenoptera venom allergic individuals.

Background
Health-Related Quality of Life (HRQoL) and the psychological burden of allergic diseases has been increasingly studied (1). The use of patient-reported outcomes in the assessment of allergic diseases is currently recommended, both in clinical studies and in daily practice, as they provide a better understanding of the patient subjective assessment of his/her health condition and they estimate the effects of new interventions from the patient’s perspective (1). Allergic diseases, such as asthma (2), rhinitis (3) and particularly food allergy (4), have a significant burden on quality of life and are associated with relevant direct, indirect, and also intangible costs (5). Hymenoptera venom allergy is a rare, but potentially life-threatening disease (6), and therefore, the fear of a re-sting and new systemic reactions may have a profound impact on HRQoL. The potential life threatening systemic reactions to insect stings are estimated to occur in only 0.3 to 0.4% of children and 3% of adults; so the true impact on health status and the negative effects on the emotional, social and sometimes professional functioning might be underestimated (6,7). Even those individuals that are on immunotherapy for venom allergy still present long-lasting debilitating beliefs and psychological impact of a threatening systemic reaction, independent of the years they were under immunotherapy (8). Studying HRQoL in these patients will allow a better understanding of the true burden of insect venom allergy according to the severity of the reaction,
Methods

Cross-cultural translation

The cross-cultural translation of the VQLQ to Portuguese was performed, after author’s permission, by forward and backward translation of the original English questionnaire and patient testing, according to published recommendations (1). The procedures are described in figure 1. During cognitive debriefing, the participants were informed that they should report the acceptability, understandability and clarity of the questionnaire and all comments were recorded by the investigators. After review of the results of the cognitive debriefing and integration of the necessary changes, the expert committee reached a final version, VQLQ-P.

Participants and study design

Participants were selected from two sources: 1) patients that were followed in the Allergy and Clinical Immunology Department of the São João Hospital in Porto due to hymenoptera venom allergy suspicion until December 2013; 2) individuals

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**Figure 1 - Cross cultural translation procedure.**

<table>
<thead>
<tr>
<th>Forward translation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Two native speaking translators, fluent in English, produced 2 independent Portuguese versions</td>
</tr>
<tr>
<td>• An expert committee, composed by a venom allergy expert and the two translators met and reached a first combined Portuguese-language translated version (VQLQ-pv1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Backward translation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The first Consensus Portuguese-language translated version was then translated back to English by an independent English native speaker, also fluent in Portuguese</td>
</tr>
<tr>
<td>• The backtranslated version (VQLQ-bpv1) was reviewed by the author of the original VQLQ</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consensus Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The expert committee met and considering the comments from the translator and input from the author of the original VQLQ, the backtranslated version, produced a second consensus matching a Portuguese-language version of the backtranslation (VQLQ-pv2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cognitive Debriefing</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Application of the VQLQ-pv2 by a face-to-face interview to five wasp venom allergy patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Final version</th>
</tr>
</thead>
<tbody>
<tr>
<td>• After review of the results from the cognitive debriefing, integration of the necessary changes, a final consensus version was reached (VQLQ-P)</td>
</tr>
</tbody>
</table>
with hymenoptera sting history who had specific IgE measurements to wasp or bee in the records of the Immunology Lab of the same hospital, from 2008 to 2011. All individuals with ≥ 18 years that had confirmed hymenoptera venom allergy to wasp or bee (history of hymenoptera sting systemic reaction and positive IgE or skin testing to the suspected hymenoptera) were included.

A structured survey was sent by mail to the homes of all eligible individuals; it included: demographic clinical data, type of reaction and symptoms, types of treatments and their related costs, as well as the VQLQ-P, EQ-5D, the Expectations of Outcome questionnaire (EoQ), and a Visual Analogue Scale (VAS) rating the interference of hymenoptera allergy in daily life. The survey was then returned by letter or in the next follow-up visit. In addition to the information obtained in the survey, all clinical records were reviewed to evaluate if the participants had diagnostic criteria of hymenoptera allergy, to assess hymenoptera sting reaction characteristics and reported beekeeper’s activity. After analysis, the patients that met the inclusion criteria were selected. Despite being previously validated only in wasp venom allergic patients, the questionnaire was also sent to honey bee venom allergic patients, since it could be possibly used in non-beekeepers allergic to bee venom (7). Patients who were beekeepers, had beekeepers in their families or did not return the questionnaires were excluded from the analysis.

The participant selection flow chart is described in figure 2. The survey was returned by 80 patients (answer rate of 58%). A total of 49 individuals (19 with wasp venom and 30 with bee venom allergy) were included in the analysis. The characteristics of the included participants are described in table 1. There were no sig-

**Figure 2 - Flowchart of the study participants. (VAS-visual analogue scale: EoQ-expectation of outcome questionnaire).**

### Table 1 - Demographic and clinical characteristics of the studied population.

<table>
<thead>
<tr>
<th>Participants (n = 49)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median [IQR]</td>
<td>47 [38;56]</td>
</tr>
<tr>
<td>Gender, female</td>
<td>21 (43)</td>
</tr>
<tr>
<td>School education</td>
<td></td>
</tr>
<tr>
<td>≤ 4 years</td>
<td>12 (25)</td>
</tr>
<tr>
<td>≥ 5 to 9 years</td>
<td>14 (29)</td>
</tr>
<tr>
<td>&gt; 9 to ≤ 12 years</td>
<td>16 (33)</td>
</tr>
<tr>
<td>&gt; 12 years</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Confirmed hymenoptera allergy</td>
<td></td>
</tr>
<tr>
<td>Bee</td>
<td>30 (61)</td>
</tr>
<tr>
<td>Wasp</td>
<td>19 (39)</td>
</tr>
<tr>
<td>Total IgE, UI/L, median [IQR]</td>
<td>90.0 [39.3; 148.3]</td>
</tr>
<tr>
<td>Wasp sIgE, kU/L, median [IQR]</td>
<td>0.9 [0.4;6.6]</td>
</tr>
<tr>
<td>Bee sIgE, kU/L, median [IQR]</td>
<td>2.1 [0.4;10.4]</td>
</tr>
<tr>
<td>Atopy</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Asthma</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>12 (25)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Severity of the systemic reaction (Müller)</td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Grade II</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Grade III</td>
<td>18 (37)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>16 (33)</td>
</tr>
<tr>
<td>Under venom Immunotherapy</td>
<td>32 (65)</td>
</tr>
<tr>
<td>Bee</td>
<td>20 (62)</td>
</tr>
<tr>
<td>Wasp</td>
<td>12 (38)</td>
</tr>
</tbody>
</table>

Results expressed as n (%), except if otherwise specified. IQR: interquartile range; sIgE: specific IgE.

The translated version of VQLQ-P (Online supplementary file 1) was used to measure HRQoL in wasp and non-beekeeper bee venom allergic individuals. The VQLQ-P has 14 questions. Each question is rated from 1 to 7 (1 the lowest and 7 the highest quality of life score). The scores are added and divided by the
number of items, excluding five questions (10 to 14) that have the option “does not apply” and are not counted. Expectation of Outcome questionnaire (EoQ) (Online supplementary file 2) was used for comparison and validation purposes (7). This tool was previously used in the development of VQLQ as, in a patient who had sting anaphylaxis, the expected outcome of future stings interferes with quality of life and might be an important target for intervention. This questionnaire includes 2 questions with a 7-point scale in which patients are asked to indicate their expectation regarding the outcome of a future sting. A visual analogue scale was added to score the level of hymenoptera allergy interference in daily life, questioning “Do you think your insect allergy interferes with your daily life?” with a score ranging from 0 (no interference) to 10 (maximal interference). The EQ-5D, validated for the Portuguese population (10-12), is a health-related quality of life questionnaire. It comprises five dimensions (mobility, self-care, usual activities, pain / discomfort, anxiety / depression) with three levels each. It is able to define 243 different health states. It also includes a VAS reporting health-related quality of life, from zero (the worst health condition) to 100 (the best health condition). The index was calculated using the Portuguese population-based predicted preference weights for the 243 EQ-5D health states (11).

Statistical analysis
All data analyses were performed using SPSS® version 20.0 for Windows (IBM SPSS, Chicago, IL, USA). Categorical variables were described using absolute frequencies and proportions and compared using Chi-square or Fisher’s exact tests. Continuous variables were described using medians with interquartile range (IQR) and compared using the Mann-Whitney test (non-normal distribution of the included variables). To assess the internal consistency, the reliability coefficient Cronbach’s alpha was used. To test construct validity, bivariate Spearman correlations between VQLQ-P individual items and the mean of all items was determined using EoQ (individual as well as mean) and EQ-5D (individual dimensions, index and general health state VAS) as comparators. To evaluate the potential applicability of the VAS use to estimate hymenoptera allergy interference in daily life, spearman correlations were performed with VQLQ-P individual and total items, EoQ and EQ-5D parameters. To evaluate differences between the correlation coefficients of wasp and bee venom allergic individuals Fisher’ Z transformation test was applied. A p-value of < 0.05 was considered statistically significant.

Results
Cross-cultural translation of VQLQ-P
During the translation and back-translation procedure, doubts and corrections were raised due to slight differences in wording and different meaning of the statements. The following items were questioned: “I am moderately frightened or scared”; “check certain places for stinging insects”; “Do you feel limited in your activities...”; “How often do you become frightened, because of your allergy, when you are stung by an insect”, different interpretations and the consensus version are specified in Online supplementary table 2. At all times, if comprehensibility was not affected, the approximation with the original version was preferred. During the phase of acquisition of author’s approval no questions or corrections were raised. After reaching the consensus version, 5 participants were interviewed for cognitive debriefing. They had a mean age of 38 years, 3 were males, and all had wasp venom allergy. The following question presented some difficulties in interpretation by two participants: “How often do you, because of your allergy, check certain places for stinging insects (yellow jackets, hornets, and wasps)?”. Participants enquired if the question reported all stinging insects or specific species of wasps. As they avoided all stinging insects, it was suggested to simplify the statement. Therefore, in the final reconciliation phase, the expert committee agreed to simplify the examples to wasp and introduce the term bee, as participants could not distinguish a bee from a wasp at first sight. No more issues were reported or changes suggested by the participants of the cognitive debriefing. The final version of VQLQ-P is presented in Online supplementary file 1.

Internal consistency of the VQLQ-P
The Cronbach α of the 14 items was 0.85 for those with confirmed hymenoptera allergy, and higher for those with wasp venom allergy (0.88) than for bee venom allergic patients (0.83).

External consistency of the VQLQ-P
The Spearman correlations between VQLQ-P items and the expectation of outcomes are shown in table 2. The correlation coefficient (r) between the total score of the VQLQ-P and the mean of the 2 questions from the EoQ was 0.71, p < 0.01. The correlation remained significant when analyzing the individuals that were on venom immunotherapy (0.74, p = 0.01). In patients with a wasp venom allergy the correlation was higher (0.76, p < 0.01) compared to the bee venom allergic patients (0.67, p < 0.01). However, there was no significant difference between these correlations (z = 0.58, p = 0.56). The global mean score of VQLQ-P was significantly correlated with EQ-5D index (r = -0.34, p < 0.05) and with the usual activities (r = 0.48, p < 0.01) and the anxiety / depression (r = 0.49, p < 0.01) dimensions of the same questionnaire. No significant correlations were found with EQ-5D mobility (r = 0.11), self-care (r = 0.22) or pain / discomfort (r = 0.21) dimensions. When considering only those with wasp venom al-
Regarding the VAS assessing interference of hymenoptera allergy in patient’s daily life it showed a significant correlation with the VQLQ-P mean score ($r = 0.68$, $p < 0.01$), as demonstrated in figure 3 and with specific questions of the questionnaire (table 3). No significant correlation was seen between the VAS reporting health-related state included in the EQ-5D and the VQLQ-P mean score ($r = -0.20$, $p = 0.29$).

<table>
<thead>
<tr>
<th>VQLQ-P item</th>
<th>Expectation of Outcome Questionnaire item 1</th>
<th>Expectation of Outcome Questionnaire item 2</th>
<th>Mean score of 1 and 2</th>
<th>VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.6641</td>
<td>0.3921</td>
<td>0.5141</td>
<td>0.6421</td>
</tr>
<tr>
<td>2</td>
<td>0.5711</td>
<td>0.3972</td>
<td>0.4741</td>
<td>0.6151</td>
</tr>
<tr>
<td>3</td>
<td>0.3602</td>
<td>0.3883</td>
<td>0.4172</td>
<td>0.300</td>
</tr>
<tr>
<td>4</td>
<td>0.6921</td>
<td>0.4972</td>
<td>0.6081</td>
<td>0.4802</td>
</tr>
<tr>
<td>5</td>
<td>0.5021</td>
<td>0.4561</td>
<td>0.4851</td>
<td>0.4661</td>
</tr>
<tr>
<td>6</td>
<td>0.4521</td>
<td>0.2791</td>
<td>0.3841</td>
<td>0.314</td>
</tr>
<tr>
<td>7</td>
<td>0.6651</td>
<td>0.5651</td>
<td>0.6401</td>
<td>0.7131</td>
</tr>
<tr>
<td>8</td>
<td>0.6791</td>
<td>0.5121</td>
<td>0.6131</td>
<td>0.5881</td>
</tr>
<tr>
<td>9</td>
<td>0.7051</td>
<td>0.5301</td>
<td>0.6381</td>
<td>0.5991</td>
</tr>
<tr>
<td>10</td>
<td>0.2601</td>
<td>0.1021</td>
<td>0.1501</td>
<td>0.156</td>
</tr>
<tr>
<td>11</td>
<td>0.0491</td>
<td>0.0571</td>
<td>0.0531</td>
<td>0.117</td>
</tr>
<tr>
<td>12</td>
<td>0.4891</td>
<td>0.2941</td>
<td>0.4192</td>
<td>0.5341</td>
</tr>
<tr>
<td>13</td>
<td>0.5001</td>
<td>0.4311</td>
<td>0.5251</td>
<td>0.4072</td>
</tr>
<tr>
<td>14</td>
<td>0.4102</td>
<td>0.2891</td>
<td>0.3481</td>
<td>0.4372</td>
</tr>
<tr>
<td>Mean (1-14)</td>
<td>0.6611</td>
<td>0.6451</td>
<td>0.7081</td>
<td>0.6201</td>
</tr>
<tr>
<td>Wasp venom allergic participants (n = 19)</td>
<td>Mean (1-14) 0.6381 0.7121 0.7581 0.6141</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bee venom allergic participants (n = 30)</td>
<td>Mean (1-14) 0.6671 0.6031 0.6691 0.7561</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 p < 0.01; 2 p < 0.05

**Table 3 - External Validity of VQLQ-P questionnaire: Spearman correlation coefficients between the mean VQLQ-P score and EQ-5D dimensions and Index.**

<table>
<thead>
<tr>
<th>EQ-5D dimensions</th>
<th>Mean VQLQ-P (1-14)</th>
<th>mobility</th>
<th>self-care</th>
<th>usual activities</th>
<th>pain / discomfort</th>
<th>anxiety / depression</th>
<th>EQ-5D Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 49)</td>
<td>0.117</td>
<td>0.228</td>
<td>0.4821</td>
<td>0.210</td>
<td>0.4941</td>
<td>-0.3352</td>
<td></td>
</tr>
<tr>
<td>Wasp venom allergy (n = 19)</td>
<td>0.237</td>
<td>0.344</td>
<td>0.5531</td>
<td>0.445</td>
<td>0.5611</td>
<td>-0.5122</td>
<td></td>
</tr>
<tr>
<td>Bee venom allergy (n = 30)</td>
<td>0.000</td>
<td>0.000</td>
<td>0.4152</td>
<td>0.034</td>
<td>0.4122</td>
<td>-0.198</td>
<td></td>
</tr>
</tbody>
</table>

1 p < 0.05; 2 p < 0.01
The Vespid Allergy Quality of Life Questionnaire - cultural adaptation and translation to Portuguese

This is the first tool translated into Portuguese to evaluate quality of life in wasp venom allergic individuals. The procedure of translation and cultural adaptation followed the recommendations of the GA2LEN guidelines (1). Another strength of our study is that the translated questionnaire was compared with other quality of life measurements, namely with the widely used health-related quality of life measurement, the EQ-5D, the Expectation of Outcome questionnaire, previously used in the development and validation of the original VQLQ, and also with VAS. In line with previous studies that suggested the VQLQ could be suitable for bee venom allergic individuals (7), we also evaluated allergic individuals that were not beekeepers and did not have relatives with beekeeping activities. Although the questionnaire was not validated to this specific group, it also showed good correlation with other quality of life outcome measurements.

Our study has some limitations, namely a small sample size. Due to its wide recruitment strategy, including all individuals followed in our Hymenoptera Allergy Unit and also those who had a past positive IgE to wasp or bee venom, we had a low response rate (58%). Furthermore, as only those with a confirmed diagnosis were included, the number of selected participants was even smaller. However, a strong and significant correlation was still found. A visual analogue scale was also used to evaluate the interference of hymenoptera allergy in daily life and, despite not being previously validated, it showed a good correlation with the VQLQ-P and EoQ. The cross-sectional design of this study did not allow to establish if this tool can measure a change in quality of life with an intervention, namely venom immunotherapy (VIT). Nonetheless, the original questionnaire had previously measured a clinically important improvement in health-related quality of life with VIT (9). Therefore, it is likely that VQLQ-P may also be used to measure VIT outcomes in Portuguese patients. When evaluating the correlation between each of the questions and the EoQ, there were some items that presented non-significant or significant mild correlations, namely those related to vigilance in places where individuals might be in contact with wasps or bees. This could be due to the small sample size which lacked the power to adequately evaluate these correlations. Another possible explanation, previously reported in the literature (7), is that the level of vigilance might not be so significant in individuals living in urban environments, leading to weaker correlations in these items, when comparing with those that live in rural places. However, in our study no data is available on the area of residence and we could not test this hypothesis. Furthermore, individuals with hymenoptera venom allergy might intentionally avoid places where the probability of contact with wasps or bees is higher, therefore choosing vacations, hobbies and places where they feel they do not need to be so alert. The environment interaction with stress and anxiety is particularly

**Figure 3** - Correlation between the Visual Analogue Scale assessing hymenoptera allergy interference with daily life and VQLQ-P mean score ($r = 0.68$, $p < 0.01$).

<table>
<thead>
<tr>
<th>VAS</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>VQLQ-P score</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
</tr>
</tbody>
</table>

**Table 2**. The results from the VAS also correlated with each of the EoQ specific questions ($r = 0.64$ and $r = 0.56$ for questions 1 and 2, respectively; $p < 0.01$) and the mean EoQ score ($r = 0.62$, $p < 0.01$). No significant correlation was found between this VAS and the one assessing global health-related state from EQ-5D ($r = -0.12$, $p = 0.610$), but a mild correlation was noticed with the activity and anxiety dimensions ($r = 0.42$, $r = 0.41$, $p = 0.05$; respectively).

When evaluating the mean VQLQ-P there were no differences between the grades of reaction to the hymenoptera sting, genders or being on venom-specific immunotherapy.

**Discussion**

The translated and culturally adapted Portuguese version of the Vespid Allergy Quality of Life Questionnaire showed a good cross-sectional correlation with the Expectation of Outcome questionnaire as well as EQ-5D, a health-related quality of life measure instrument. In the non-beekeeper bee venom-allergic patients a good correlation was also seen. The applied VAS presented a good correlation with the VQLQ-P and EoQ. This translated version of the Vespid Allergy Quality of Life Questionnaire and the VAS evaluating the hymenoptera allergy interference with daily life appear to be two easy tools to evaluate quality of life impairment in Portuguese hymenoptera venom allergic individuals. However, a longitudinal evaluation of their applicability is needed in non-beekeeper allergic patients.
addressed in VQLQ, however, for precise characterization, comparative studies with different environmental settings and populations may be needed, as previously suggested (13).

The Vespid Allergy Quality of Life Questionnaire was originally developed in Dutch (7) and latter translated and validated in English (7), German (13), Polish (14) and Spanish (15). All the cross cultural translated versions showed a good internal consistency, as our Portuguese version. We did not find a significant correlation with age, grade of reaction or VIT. Conflicting results have been seen for gender, with some studies reporting a stronger impact in quality of life in women versus men (16) and others reporting otherwise (15). Another study found a stronger correlation with the severity of reaction, in which those with a severe anaphylaxis had greater impairment in quality of life (14). Our study showed a strong positive correlation (0.8) between the mean score of VQLQ-P and the mean EoQ, which was similar to the German and Dutch versions (0.7), but higher than the Spanish version (0.5). This may be explained by the inclusion of individuals with allergic reactions to Apis, Vespuila and Polistes in the Spanish study (15). Nevertheless, we also found a good correlation between these tools in non-beekeeper bee venom allergic individuals. A good correlation was reported with other measures of QoL, namely with the WHOQOL-BREF, used for comparison in the German validation study, particularly with the “physical well-being” and “psychological well-being” dimensions, and with the SF-12, used in the Spanish study (15). This was reproduced in our study with a good correlation seen with the usual activities and anxiety / depression dimensions of the EQ-5D. The resemblance with a health-related quality of life measure might support the use of VQLQ-P to evaluate the cost-effectiveness of future intervention studies in hymenoptera venom allergic individuals.

Venom immunotherapy has been shown to improve health-related quality of life in wasp venom allergic patients (9). In another study, even in venom allergic patients on VIT, debilitating beliefs associated with the fear of a systemic reaction were seen (8). Two recent studies showed that quality of life (evaluated by VQLQ) improved significantly in hymenoptera venom allergy individuals currently on VIT (16,17). Therefore, the VQLQ may be particularly relevant when evaluating VIT’s cost-effectiveness.

A study analyzing the economic burden linked to VIT, showed that it is associated with a cost of up to 23 million per year (18). This systematic review, focusing in the life saving aspect of VIT, was limited by the poor quality of the included studies and the lack of studies evaluating HRQoL. Therefore, as expected, it was associated with a very high cost per QALY gained (18). This strategy to evaluate cost-effectiveness, using only survival data, has been criticized as the specific effects on quality of life should also be taken into account (19). In this way, VQLQ-P can have a role in the patient-centered approach to decision-making when initiating VIT. Recently, VIT is no longer covered by the health care system in Portugal and the cost of the treatment is totally supported by the patient. The evaluation of specific QoL in hymenoptera venom allergic patients could be useful to evaluate QALY in this population and thereafter the need for the health care system to support this treatment in venom allergic patients. For this questionnaire to be further used, a longitudinal validation is needed with a larger sample and using a multi-centered approach.

In conclusion, the Portuguese version of VQLQ and the hymenoptera allergy interference in daily life VAS can be used in future research and clinical contexts to evaluate quality of life in wasp venom allergic patients. Despite not being previously validated in non-beekeeper bee venom allergic patients, VQLQ-P and VAS also showed to have a good reliability in this setting. The application of VQLQ-P in the initial approach to a hymenoptera venom-allergic patient, may also guide the allergist to actively promote reassurance of the patient and provide support in the decision to start venom specific immunotherapy.

References
Evaluation of pulmonary complications in patients with primary immunodeficiency disorders

Introduction

Primary immunodeficiency diseases (PID) are a group of more than 200 rare, chronic disorders, in which a part or functions of the immune system is missing or improperly working (1,2). However, defects in the immune system cause a spectrum of complications, including increased susceptibility to infection, autoimmunity and malignancy (3-5). Recurrent respiratory tract infections (RTIs) are the most common clinical manifestation of them, especially in CVID (6), XLA (7), HlgM (8,9) and selective IgA deficiency (10). The most common RTIs include upper airway infections (e.g. otitis media and sinusitis) and lower airway infections (e.g. bronchial abnormalities, especially bronchiectasis, interstitial lung diseases, obstructive lesions and chronic obstructive pulmonary disease). Lower respiratory tract complications are generally considered to be more significant.
Evaluation of pulmonary complications in patients with primary immunodeficiency disorders

and more particular for PIDs and their prognosis (11). Clinical warning symptoms of PID would facilitate early diagnosis and appropriate treatment, and can prevent later severe outcomes such as mastoiditis and bronchiectasis. Retrospective studies in patients with PIDs have shown the existence of bronchiectasis, peribronchial thickening, air trapping, lung volume reduction, atelectasis, follicular bronchiolitis and parenchyma nodule, which lead to more clinical studies of pulmonary complications in PIDs (12,13). Bronchiectasis and bronchial wall thickening were the most frequent pulmonary complications in CVID patients (13). It is demonstrated that early diagnosis along with adequate immunoglobulin replacement therapy in patients with primary antibody deficiencies, could reduce the number of pulmonary infections (14). Therefore, the increasing of knowledge in this field is critical for the achievement of optimal patient management and for the increase of life expectancy of PIDs. Even though several studies have reported pulmonary complications in patients with different PID disorders, there are only a few reports comparing the pulmonary complications between these diseases. The aims of this study were to investigate the prevalence of pulmonary complications in patients with PID, and to evaluate the probable associations between pulmonary complications and other clinical and immunological features in these patients, in order to raise the known science in this field.

Material and Methods

Patients

This cross sectional study was performed in Immunodeficiency Clinic at the Children’s Medical Center affiliated to Tehran University of Medical Sciences during 2013-2014. A total of 204 patients with PID (94 with CVID, 41 with XLA, 51 with HIES, 15 with HlGM, 3 with SCID), who were diagnosed and treated at this center, agreed to participate in this study. It should be noted that written informed consent was obtained from all patients.

Demographic and clinical information

An appropriate questionnaire was developed to be completed by patients, interviewing for demographic information including age, sex, type of PID, age at onset of symptoms, age at diagnosis and history of respiratory and pulmonary infections as well as lung complications. Diagnostic delay was defined as the time between the onset of symptoms and the time of diagnosis. Moreover, for each patient, the total number of pneumonia episodes before and after diagnosis was recorded. The diagnosis of pneumonia was based on international criteria by using clinical, radiological and laboratory evidence of lower respiratory tract infections.

Pulmonary function tests

Pulmonary function test (PFT) was evaluated according to the American Thoracic Society recommendations, using a computerized pneumotachograph (Jaeger, Wurzburg, Germany) in PID patients who were six years and older and cooperative, with patients tested in the seated position (within a volume displacement body plethysmograph). FEV1, FVC, FEV1/FVC and maximal mid-expiratory flow (MMEF 25-75%) were recorded for each tested patients.

Chest radiographs and HRCT scanning

Standard postero-anterior and lateral chest X-ray, as well as high-resolution computed tomography (HRCT) scans, were obtained for each patient. Radiographs were evaluated to detect interstitial involvement of upper, middle and lower areas of both lungs. To confirm the presence of chronic lung disease, the HRCT was performed in patients who had persistent symptoms for more than four weeks. HRCT was evaluated using the modified Bhalla scoring method to check the presence and severity of different parameters, including: 1, the presence and extent of bronchiectasis; 2, the average severity of bronchial dilatation; 3, bronchial wall thickness; 4, the extent of decreased attenuation of the lung parenchyma; 5, the presence or absence of mucus within the large airways; 6, the extent of bronchial wall collapse; and 7, the extent of tracheal collapse. The mentioned parameters were scored separately for each lung lobes and the lingual. The total lung score was derived by summing the lobar grades. Bronchiectasis was determined as bronchial dilatation, often with thickening of the walls.

Bronchoscopy and bronchoalveolar lavage

Bronchoscopy and BAL was performed by a pediatric pulmonologist as previously described (15), in the PID patients who showed in their chest X-ray persistent respiratory symptoms, including refractory pneumonia, persistent infiltration and resistant atelectasis. The recovered lavage fluid was evaluated cytologically (global and specific cytology) by using light microscopy at × 1000 for differential cell count of lymphocytes, macrophages, neutrophils and eosinophils. Finally, pulmonary needle biopsy was obtained from patients with persistent respiratory symptoms who did not response to treatments; also, other mentioned work up could not help determine the etiology of pulmonary complications.

Statistical Analysis

Clinical information, including PFT, HRCT and BAL results, was compared among the patient groups. Fisher’s exact test and
Pulmonary infections before and after diagnosis

Pulmonary infections, particularly pneumonia, were the most frequent clinical manifestation in all PID patients. Before diagnosis and immunoglobulin replacement therapy, 73 CVID patients (78%), 34 HIES patients (67%), 25 XLA patients (60%), and 15 HIgM patients (100%) experienced at least one episode of pneumonia (P = 0.014). The characteristics of the patients with a history of pneumonia are shown in Table 3. In order to adjust the probable effect of delayed diagnosis of pneumonia incidence rate, patients were stratified into those with delays of < 6 years and those with delays > 6 years. Comparison of the pneumonia incidence rates within the stratified groups, showed that there were significantly greater numbers of episodes of pneumonia in HIgM, XLA and CVID patients with delayed diagnosis < 6 years (P = 0.024).

chi-square tests were used for 2 × 2 comparison of categorical variables, whereas t-tests and one-way ANOVA were used to compare numerical variables. Statistical analysis was performed using the SPSS software package, version 21 (SPSS Inc., Chicago, IL, USA). A P-value < 0.05 was considered significant.

Results

Characteristics baseline of the patients

There were 204 PID patients (137 male, and 67 female), aged 3-66 years, who had been diagnosed with PIDs, including 94 (46.1%) with CVID, 41 (20.1%) with XLA, 51 (25.0%) with HIES, 15 (7.3%) with HIgM, 3 (1.5%) with SCID (Table 1). Immunological data, including serum immunoglobulin levels and lymphocyte subset percent at the time of diagnosis, are shown in Table 2.

### Table 1 - Characteristics of the patients with PID (n = 204).

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Gender (Male / Female)</th>
<th>Age at the study time (y/o)</th>
<th>Age at onset of symptoms (y/o)</th>
<th>Age at the time of diagnosis (y/o)</th>
<th>Delayed diagnosis time (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Min - Max</td>
<td>Median (IQR)</td>
<td>Min - Max</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>CVID</td>
<td>94</td>
<td>54/40</td>
<td>10-66</td>
<td>25 (11.75)</td>
<td>0-46</td>
<td>2 (6)</td>
</tr>
<tr>
<td>XLA</td>
<td>41</td>
<td>41/0</td>
<td>6-43</td>
<td>22 (11.10)</td>
<td>0-6</td>
<td>1 (1.20)</td>
</tr>
<tr>
<td>HIES</td>
<td>51</td>
<td>25/26</td>
<td>4-45</td>
<td>15 (15)</td>
<td>0-28</td>
<td>0 (1)</td>
</tr>
<tr>
<td>HIgM</td>
<td>15</td>
<td>14/1</td>
<td>8-39</td>
<td>15 (14)</td>
<td>0-7</td>
<td>1 (1)</td>
</tr>
<tr>
<td>SCID</td>
<td>3</td>
<td>3/0</td>
<td>3-5</td>
<td>3 (.)</td>
<td>0-1</td>
<td>0 (.)</td>
</tr>
</tbody>
</table>

### Table 2 - Immunologic features of PID patients at diagnosis stage.

<table>
<thead>
<tr>
<th></th>
<th>CVID (Mean ± SD)</th>
<th>HIES (Mean ± SD)</th>
<th>HIgM (Mean ± SD)</th>
<th>XLA (Mean ± SD)</th>
<th>SCID (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (/µL)</td>
<td>8774.1 ± 3602.9</td>
<td>13699.7 ± 8998.0</td>
<td>8683.3 ± 5857.4</td>
<td>5601.8 ± 3632.5</td>
<td>6680 ± 3056.5</td>
</tr>
<tr>
<td>Lymphocyte (%)</td>
<td>34.1 ± 16.2</td>
<td>39.6 ± 21.1</td>
<td>54.5 ± 23.4</td>
<td>47.6 ± 21.8</td>
<td>6.7 ± 4.2</td>
</tr>
<tr>
<td>CD3 (% of lymphocytes)</td>
<td>71.5 ± 16.4</td>
<td>74.3 ± 18</td>
<td>69.2 ± 12.3</td>
<td>86.9 ± 9</td>
<td>16.7 ± 24.8</td>
</tr>
<tr>
<td>CD4 (% of lymphocytes)</td>
<td>32.2 ± 14.4</td>
<td>50 ± 12.5</td>
<td>33.7 ± 12.4</td>
<td>41.3 ± 14.9</td>
<td>1.7 ± 1.2</td>
</tr>
<tr>
<td>CD8 (% of lymphocytes)</td>
<td>39.6 ± 13.8</td>
<td>26 ± 8.3</td>
<td>30 ± 12.6</td>
<td>43 ± 19.8</td>
<td>6 ± 10.4</td>
</tr>
<tr>
<td>CD19 (% of lymphocytes)</td>
<td>7.6 ± 5.3</td>
<td>14.5 ± 2.1</td>
<td>15.6 ± 7.4</td>
<td>1.2 ± 1.6</td>
<td>0.7 ± 0.6</td>
</tr>
<tr>
<td>IgG (mg/L)</td>
<td>149.4 ± 134.1</td>
<td>1359.8 ± 7898.8</td>
<td>137 ± 158.0</td>
<td>43.2 ± 67.4</td>
<td>116.7 ± 116.5</td>
</tr>
<tr>
<td>IgA (mg/L)</td>
<td>17.7 ± 31.4</td>
<td>116.2 ± 86.2</td>
<td>26.5 ± 38.5</td>
<td>7 ± 9.1</td>
<td>1.7 ± 1.5</td>
</tr>
<tr>
<td>IgM (mg/L)</td>
<td>27.7 ± 33.1</td>
<td>135.8 ± 119.2</td>
<td>419.3 ± 346.3</td>
<td>13.2 ± 19.7</td>
<td>4.7 ± 3.8</td>
</tr>
</tbody>
</table>
Evaluation of pulmonary complications in patients with primary immunodeficiency disorders

We evaluate lung complications in 149 PID patients by HRCT which bronchiectasis was confirmed in 56 (37.6%) patients. The age of patients with bronchiectasis (median age 13 years, range 41 years) differed from those of non-bronchiectasis patients (median age 6.7 years, range 52.90 years). Bronchiectasis was showed in 9 (42.9%) of XLA, 6 (11.8%) of HIES, 3 (21.4%) of HIgM and 38 (62.3%) of CVID patients. Our results showed a correlation between delay in diagnosis and the frequency of bronchiectasis in PID patients, so delay in diagnosis in bronchiectatic patients was higher than non-bronchiectatic patients. This difference was significant in HIgM (P = 0.007) and HIES (P = 0.008) patients; however, it wasn’t significant in CVID (P = 0.07) and XLA (P = 0.11) patients. Moreover, the prevalence of bronchiectasis in CVID patients was more than HIgM, HIES and XLA patients. Although the difference was statistically significant for XLA and HIES (P = 0.029, P = 0.001, respectively), but was not significant for HIgM (P = 0.137). For evaluation of severity of bronchiectasis, HRCT data were independently evaluated by an expert radiologist using a modified Bhalla scoring system. In this evaluation, the presence,

Table 3 - Comparison of pneumonia episodes in different PID patients.

<table>
<thead>
<tr>
<th></th>
<th>CVID</th>
<th>XLA</th>
<th>HIES</th>
<th>HIgM</th>
<th>SCID</th>
<th>Value&lt;sup&gt;b&lt;/sup&gt; (P-Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients with pneumonia (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delay diagnosis &lt; 6 y</td>
<td>43/58 (74.1)</td>
<td>21/37 (56.0)</td>
<td>12/23 (52.2)</td>
<td>12/12 (100)</td>
<td>3/3 (100)</td>
<td>13.129 (0.007)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delay diagnosis &gt; 6 y</td>
<td>30/36 (83.3)</td>
<td>4/4 (100)</td>
<td>22/28 (78.6)</td>
<td>3 (100)</td>
<td>0 (0.0)</td>
<td>0.955 (0.876)</td>
</tr>
<tr>
<td></td>
<td>73/94 (77.7)</td>
<td>25/41 (61.0)</td>
<td>34/51 (66.7)</td>
<td>15/15 (100)</td>
<td>3/3 (100)</td>
<td>12.198 (0.011)</td>
</tr>
<tr>
<td>Total patients</td>
<td>55/94 (58.5)</td>
<td>18/41 (43.9)</td>
<td>46/51 (90.2)</td>
<td>9/15 (60.0)</td>
<td>3/3 (100)</td>
<td>27.206 (0.001)</td>
</tr>
<tr>
<td>After diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>Test between positive and negative pneumonia episodes in different PID patients. a, positive pneumonia episodes/tested for pneumonia; b, Fisher’s Exact Test.

The majority of patients with PID were receiving intravenous immunoglobulin (IVIG) at a dose of 400-600 mg/kg/month and also prophylactic antibiotics according to the type of PIDs. The frequency of pneumonia after treatment decreased significantly in CVID (P = 0.001) and HIgM (P = 0.01) patients. In addition, the frequency of pneumonia was decreased in XLA cases; however, it wasn’t significant (P = 0.1).

Pulmonary function tests

Excluding children under the age of 6 years, who cannot cooperate appropriately for spirometry, PFT was performed for 54 patients with CVID, 20 patients with XLA and 9 patients with HIgM. 57.4% CVID patients, 55% XLA patients, and 33.3% HIgM patients, had abnormal PFT results (table 4). There were no significant differences between the frequency of pneumonia occurrence in patients with different patterns of spirometry (P = 0.5). Moreover, there were no significant differences in patterns of PFT between CVID, HIgM and XLA patients (P = 0.398). Pattern of obstruction in patients with bronchiectasis was prominently more than those without bronchiectasis (P = 0.005).

HRCT scanning

We evaluate lung complications in 149 PID patients by HRCT which bronchiectasis was confirmed in 56 (37.6%) patients. The age of patients with bronchiectasis (median age 13 years, range 41 years) differed from those of non-bronchiectasis patients (median age 6.7 years, range 52.90 years). Bronchiectasis was showed in 9 (42.9%) of XLA, 6 (11.8%) of HIES, 3 (21.4%) of HIgM and 38 (62.3%) of CVID patients. Our results showed a correlation between delay in diagnosis and the frequency of bronchiectasis in PID patients, so delay in diagnosis in bronchiectatic patients was higher than non-bronchiectatic patients. This difference was significant in HIgM (P = 0.007) and HIES (P = 0.008) patients; however, it wasn’t significant in CVID (P = 0.07) and XLA (P = 0.11) patients. Moreover, the prevalence of bronchiectasis in CVID patients was more than HIgM, HIES and XLA patients. Although the difference was statistically significant for XLA and HIES (P = 0.029, P = 0.001, respectively), but was not significant for HIgM (P = 0.137). For evaluation of severity of bronchiectasis, HRCT data were independently evaluated by an expert radiologist using a modified Bhalla scoring system. In this evaluation, the presence,

Table 4 - PFT pattern in patients with PADs.

<table>
<thead>
<tr>
<th>PADs</th>
<th>Abnormal PFT</th>
<th>Normal PFT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obstructive</td>
<td>Restrictive</td>
<td>Mixed</td>
</tr>
<tr>
<td>CVID (n = 54)</td>
<td>8 (14.8%)</td>
<td>13 (24.0%)</td>
<td>10 (18.6%)</td>
</tr>
<tr>
<td>HIgM (n = 9)</td>
<td>0</td>
<td>0</td>
<td>3 (33.3%)</td>
</tr>
<tr>
<td>XLA (n = 20)</td>
<td>1 (5.0%)</td>
<td>6 (30.0%)</td>
<td>4 (20.0%)</td>
</tr>
</tbody>
</table>
Recurrent pulmonary infections are the major cause of morbidity and mortality among patients suffering from different forms of PIDs both in children and adults (2). There are a few studies which have evaluated respiratory complications, bronchiectasis, BAL and lung biopsy in different types of PIDs, simultaneously.

Recent studies have reported that about 75-84% of CVID patients and 62-82.5% of XLA patients had at least one pneumonia episode before diagnosis and treatment (17-20). In this study, our results showed that 78% of CVID, 67% of HIES, 60% of XLA and all of HIgM patients had a history of pneumonia episodes before the treatment. However, in our previous study 77.6% of CVID and 82% of XLA patients had at least one pneumonia episode before the treatment (1). Moreover, in other studies Grimbacher et al. and Winkelstein et al. reported that 77% of patients with HIES (21) and 81% of patients with HIgM (22) had at least one pneumonia episode before treatment, respectively. It is proposed that the delayed diagnosis and treatment leads to chronic lung diseases in PID patients. However, in this study we found that less delayed diagnosis is associated with increased number of pneumonias. We think this appears to be disease-specific, with SCID and XLA percentages different from CVID and HIES syndrome.

In PADs, the pneumonias are typically caused by encapsulated bacteria. In X-linked HIGM, pathogens are similar to the patients with combined immunodeficiencies. The underlying infectious cause of the pneumonias includes encapsulated bacteria, cytomegalovirus, histoplasmosis, and P. jirovecii. Fungal pneumonias caused by Candida, Cryptococcus, and Histoplasma can be also found (23,24). In SCID, respiratory tract is the most common site of infections and the most frequently involved microorgan-

**Table 5 - Cellular and Microbiological Analysis of BAL Fluid.**

<table>
<thead>
<tr>
<th>PN</th>
<th>Disease</th>
<th>Cell counts (10^3)/ml</th>
<th>Neu (%)</th>
<th>Lym (%)</th>
<th>Molecular evaluation</th>
<th>PCP Staining</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CVID</td>
<td>600</td>
<td>85</td>
<td>10</td>
<td>Neg</td>
<td>Neg</td>
<td>Haemophilus influenzae</td>
</tr>
<tr>
<td>2</td>
<td>CVID</td>
<td>400</td>
<td>70</td>
<td>20</td>
<td>Neg</td>
<td>Neg</td>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td>3</td>
<td>HIgM</td>
<td>250</td>
<td>16</td>
<td>11</td>
<td>Neg</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>HIgM</td>
<td>320</td>
<td>30</td>
<td>55</td>
<td>Pos</td>
<td>Neg</td>
<td>Klebsiella pneumoniae</td>
</tr>
<tr>
<td>5</td>
<td>HIgM</td>
<td>230</td>
<td>62</td>
<td>30</td>
<td>Neg</td>
<td>Neg</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>6</td>
<td>SCID</td>
<td>180</td>
<td>85</td>
<td>7</td>
<td>Pos</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>SCID</td>
<td>175</td>
<td>80</td>
<td>7</td>
<td>Neg</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>SCID</td>
<td>250</td>
<td>80</td>
<td>5</td>
<td>Neg</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>SCID</td>
<td>150</td>
<td>90</td>
<td>3</td>
<td>Neg</td>
<td>Neg</td>
<td></td>
</tr>
</tbody>
</table>

PN: Patient number; Neu: Neutrophils; Lym: Lymphocyte; PCP: Pneumocystis pneumonia; CN: Congenital neutropenia; CMV: Cytomegalovirus; HSV: herpes simplex virus; EBV: Epstein-Barr virus; TB: Tuberculosis.

The cytological and microbiological analysis of BAL fluid is shown in Table 5. Moreover, lung biopsy was performed in 7 patients with refractory respiratory symptoms. In 5 CVID patients, one case had granuloma, 3 cases had lymphoid interstitial pneumonitis and 1 case had maltoma. Interstitial lung disease was also seen in lung biopsy of two patients with SCID and HIGM syndrome.

**Discussion**

Respiratory complications present a significant cause of morbidity and mortality among patients suffering from different forms of PIDs. They can affect primarily either upper airways such as sinusitis and otitis media or lower respiratory tract such as pneumonia, bronchitis, bronchiectasis, and interstitial lung diseases (ILDs) (2). Patients with cellular immunodeficiency with symptoms begin at an early age, and are diagnosed before one year of age. Patients with PADs have more frequent and early respiratory symptoms. The most common respiratory diseases are otitis media, with sinusitis and pneumonia more common in PADs and phagocytic defects. In addition, PFT showed greater impairment in patients with phagocyte defects, but no statistical significance (16).
isms are *P. jirovecii*, cytomegalovirus, adenovirus, parainfluenza virus type 3, and respiratory syncytial virus (25). In our study isolated pathogens in PAD patients were *H. Influenza* and *S. Pneumoniae*, while in SCID were *K. Pneumoniae* and *S. Aureus*. Our results showed that the rate of pneumonia after receiving IVIG reduced to 58.5% in CVID, 43.9% in XLA and 60% in HIgM. This study confirms the efficacy of IVIG to reducing the rate of pneumonia in humoral immunodeficiencies as it demonstrated previously. In a study, Dukes et al. reported that after immunoglobulin therapy in CVID patients, the frequency of pneumonia episodes were reduced from 69% to 22% after immunoglobulin therapy (26). In another study, Aghamohammadi et al. showed that 82% of patients with XLA presented episodes of pneumonia before diagnosis, whereas 38.4% of patients experienced pneumonia after immunoglobulin replacement therapy (14).

Nevertheless, PID patients are prone to progressive lung disease despite optimal immunoglobulin therapy and prophylactic antibiotics (27). In our study, 57.4% of CVID patients, 55% of XLA patients and 33.3% of HIgM patients had abnormal PFT results. These results were consistent with results of Gharagozlou et al. reported decrease of FEVI and FVC to 65% and 55% in primary hypogammaglobulinemia patients, respectively. They also showed that pathological bronchial findings were observed in 13 (59%) of 22 patients: three patients showed only peribronchial thickening, and the remaining ten patients suffered from both bronchiectasis and peribronchial wall thickening (28).

It should be noted that up to 73% of CVID patients develop chronic structural pulmonary complications, of which bronchiectasis and bronchial wall thickening are most frequently detected (29). In addition, more studies noted the incidence of 7–68% of bronchiectasis and bronchial thickening in CVIDs (30,31). Our results confirmed the higher rate of bronchiectasis in CVID patients in comparison to other types of Primary Antibody Deficiency (PAD) as shown in the mentioned studies (14,30). This may cause more delay in diagnosis, which can result in more episodes of infections including pneumonia. It is demonstrated that the delay of diagnosis in patients with bronchiectasis was significantly higher than in those without bronchiectasis (28). Therefore, pulmonologist should consider PID diseases in every patient with refractory respiratory problems, because early diagnosis can reduce complications of long lasting infections in these patients.

**References**

Assessment of validity and reliability of Drug Hypersensitivity Quality of Life Questionnaire: The Dutch experience

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²Allergy and Respiratory Diseases Clinic, DIMI, University of Genoa, IRCCS AOU San Martino-IST, Genoa, Italy

Introduction

Drug hypersensitivity reactions (DHRs) are the adverse effects of drugs taken at a dose which is tolerated by normal subjects, and which clinically resemble allergy (1). DHRs represent one third of adverse drug reactions and concern more than 7% of the general population (1). Moreover, DHRs are responsible for significant morbidity and possible socioeconomic costs (2). As Health Related Quality of Life (HRQoL) has become an important outcome measure in the treatment of allergic diseases (3,4), the evaluation of HRQoL in patients with drug hypersensitivity is still a widely neglected topic. Even though almost every doctor has encountered a patient presenting with drug hypersensitivity reaction, not many physicians recognize the potential quality of life impact in patients experiencing such reaction as they often appear unexpectedly (2). One of the few studies on the psychometric profiles of patients with DHRs found that patients with drug hypersensitivity had more somatization, reduced HRQoL and more anxiety compared to the general population (5). According to the author standardized questionnaires could help to discover patients who may need psychological support (5). In 2011, the first standardized, psychometrically robust questionnaire was developed by an Italian group to measure HRQoL impact in patients with drug hypersensitivity, independent of the responsible drug (6). The Drug hypersensitivity Quality of Life Questionnaire (DrHy-Q) was initially derived from a 34-item pool and scaled down to a 15-item questionnaire and has subsequently been validated for the Italian, Turkish and Spanish population (6-8). Since its first publication, the DrHy-Q has shown to be an appropriate tool for quality-of-life research in patients with drug hypersensitivity and is able to discriminate between number of implicated drugs causing DHRs and severity of DHRs (6,7). In the Turkish population, DrHy-Q was also...
able to capture improvement of HRQoL in patients with DHR after diagnostic intervention, and provocation test for finding safe alternative drug or desensitization with culprit drug (7). Furthermore, the DrHy-Q was used to explore HRQoL in patients who experienced an anaphylactic drug reaction in an Italian study and recognized significant HRQoL impairment (9). In the Dutch setting, the DrHy-Q has not been validated yet. Also, an overview of the HRQoL in patients with DHRs across countries has not been established until now.

In this study, we translated the DrHy-Q into Dutch and performed a cross-cultural linguistic adaptation and validation to provide a clinimetrically valid tool for assessing HRQoL in patients with drug hypersensitivity in the Netherlands. We also compared the DrHy-Q scores obtained across countries to investigate cross-cultural differences in HRQoL impact of DHRs.

Methods

Validation of the DrHy-Q followed a two-step procedure:

First: Translation and Pilot Testing of DrHy-Q

The DrHy-Q is composed of 15 questions and standardized response choices arranged in a five-point Likert scale (ea. 1 ‘not at all’ to 5 ‘very much’) (6). The original Italian version of the DrHy-Q (6) was translated into Dutch using a 3-stepwise protocol (10):
1. Forward translation by two professional translators; followed by a reconciliation of the differences between the two forward translations in consultation with the investigators, resulting in a single, provisional Dutch translation. 2. Backward translation by one professional translator with no access to the original Italian version. Added ratings of the backward translation by the original developer of the questionnaire (6), in terms of clarity, common language usage, and conceptual equivalence and subsequent reconciliation of problematic items. 3. Pilot testing (n = 10) of the Dutch version of the DrHy-Q in terms of acceptance and comprehension of the questionnaire content and wording.

Second: Field Testing, Population and Validation Procedure

Design. A cross-sectional observational study was performed to determine validity and reliability of the DrHy-Q in adult patients with drug hypersensitivity. The DrHy-Q was mailed to all eligible patients (for selection of patients, see below) to be completed at home. Non-respondents received a reminder letter 3 weeks after the initial mailing. All patients who completed the first questionnaire received a second questionnaire within 10 - 14 days for re-test analysis.

Population. All patients aged 18 years and older during study inclusion, who visited the Department of Allergology at the University Medical Center Utrecht, the Netherlands, between January 2007 to November 2015 with confirmed drug hypersensitivity (n = 229) and no ongoing diagnostic involvement, were invited to participate. The diagnostic protocol for ADRs was in accordance with the standard operating procedures recommended by the European Network for Drug Allergy (11). A signed informed consent for medical record release was obtained from participating patients. Data concerning patient’s age, gender, concomitant allergic diseases, implicated drugs, symptoms of drug reaction and type of reaction according to the Coombs and Gell classification (12), were collected from patient’s medical files. The local Medical Ethics Review Commission confirmed that approval is not necessary (METC protocol nr. 15/729).

Validation procedures. The COSMIN checklist (13) was used to ascertain the methodological quality of the validation procedure and comprised two parts: construct validity and reliability. Construct validity was subdivided in structural validity, convergent validity and discriminant ability. Structural validity was assessed with confirmatory factor analysis (14). Convergent validity of the DrHy-Q was explored by administering the Dutch version of the generic HRQoL questionnaire RAND-36 (15) simultaneously. This health profile measure (16) consists of 36 items divided into nine scales, measuring functional status and well-being: physical functioning, social functioning, role functioning-physical, role functioning-emotional, mental health, vitality, bodily pain, general health and change in health (single item). The scale scores are presented in a 0 - 100-point with a higher score indicating a better HRQoL. The discriminative ability of the DrHy-Q was examined by dividing the study population into number of implicated drug hypersensitivities and severity of DHRs. The reliability of DrHy-Q was investigated by internal consistency (17) and test-retest reliability (18).

Cross-cultural differences in DrHy-Q scores

The total DrHy-Q score of the study populations in Italy (6) and Turkey (7) were compared with our Dutch DrHy-Q scores. The characteristics of implicated study participants were retrieved from the articles and unpublished data were retrieved by correspondence with the study authors.

Analyses

The DrHy-Q scores were converted to a 0 to 100 scale (formula: DrHy-Q = (Σ [items] - 15 / [75 -15]∗100), with a higher score indicating a poor disease-specific HRQoL. Missing values were imputed by single imputation using the expectation maximization algorithm (19). Structural validity was assessed by first-order confirmatory factor analyses for categorical data with chi-square goodness-of-fit test and the RMSEA descrip-
Assessment of validity and reliability of Drug Hypersensitivity Quality of Life Questionnaire: The Dutch experience

Internal consistency was measured by calculating Cronbach's alfa, with a value of ≥ 0.70 indicating adequate inter-relatedness of items (20). The test-retest reliability was assessed by calculating the intra-class correlation coefficient (ICC). ICC values were interpreted as follows: > 0.75 was excellent, 0.40-0.75 was fair to good and < 0.40 was poor (21). Descriptive statistics were used to display cross-country population differences in which DrHy-Q scores were obtained. A \( p \leq 0.05 \) was considered statistically significant. Statistical analyses were performed using SPSS 23 for Windows 8.1 (SPSS Inc., Chicago, IL, USA), with the exception of confirmatory factor analyses using Mplus Base Program 6.12 for Windows 8.1 (Muthen & Muthen, Los Angeles, CA, USA).

<table>
<thead>
<tr>
<th>Implicated drugs</th>
<th>n (%)</th>
<th>median (minimum - maximum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>62 (50.0)</td>
<td>13.3 (0 - 56.7)</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>14 (11.3)</td>
<td>15.0 (1.7 - 88.3)</td>
</tr>
<tr>
<td>Peri-operative medication(^2)</td>
<td>19 (15.3)</td>
<td>10.0 (0 - 68.3)</td>
</tr>
<tr>
<td>Steroids</td>
<td>10 (8.1)</td>
<td>11.7 (3.3 - 56.7)</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>5 (4.0)</td>
<td>10.0 (5 - 48.3)</td>
</tr>
<tr>
<td>Others(^2)</td>
<td>20 (16.1)</td>
<td>10.8 (0 - 83.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of implicated drugs</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81 (65.3)</td>
<td>8.3 (0 - 88.3)(^1)</td>
</tr>
<tr>
<td>≥ 2</td>
<td>43 (26.7)</td>
<td>18.3 (0 - 83.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of hypersensitivity reaction</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (immediate-type)</td>
<td>89 (71.8)</td>
<td>11.7 (0 - 88.3)</td>
</tr>
<tr>
<td>Type IV (delayed-type)</td>
<td>35 (28.2)</td>
<td>11.7 (0 - 76.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of symptoms of the drug hypersensitivity reaction(^1)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin symptoms</td>
<td>93 (78.8)</td>
<td>11.7 (0 - 88.3)</td>
</tr>
<tr>
<td>Angio edema</td>
<td>46 (39.0)</td>
<td>10.0 (0 - 76.7)</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>21 (17.8)</td>
<td>17.7 (3.3 - 83.3)</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>35 (29.7)</td>
<td>10.0 (0 - 88.3)</td>
</tr>
<tr>
<td>Cardiovascular symptoms</td>
<td>42 (35.6)</td>
<td>13.3 (0 - 88.3)</td>
</tr>
</tbody>
</table>

DrHy-Q: Drug Hypersensitivity Quality of Life Questionnaire; DHR: Drug hypersensitivity reaction; n: Number

\(^1\)Mann-Witney U test, significant difference between medians, \( p = 0.001 \).

\(^2\)Peri-operative medication: muscle relaxants, patent blue, chlorhexidine, morphine, remifentanil; Other drugs: radiocontrast media, vaccines, plasma expanders, local anesthetics, anticoagulants, acetaminophen, anti-epileptics, triptans, drug additives.

\(^3\)Symptoms of skin: urticaria, pruritis, maculae/papulae, blisters, pustules; Cardiovascular symptoms: drop in blood pressure, shock, anaphylaxis.
Results

Translation

The Dutch DrHy-Q was pilot tested in a sample of 8 patients with DHR visiting the Allergology department for diagnostics, equally representing men and women aged between 21 and 82 years. No unambiguity was reported in terms of acceptance or comprehension of the questionnaire content and wording. This version required no further modifications, and was used in subsequent field testing. The final version of the DrHy-Q is depicted in the appendix.

Field test: study population

A total of 229 patients were identified of whom 217 were eligible for participation. All eligible patients were invited to participate in the study of whom 124 (57%) completed the questionnaire. 65.3% of the respondents were female, with a mean age of 56.8 ± 14.0 years, range [18 - 86]. No dissimilarities in gender were detected between responders and non-responders. Non-Responders, however were significantly younger (49.9 ± 16.0) compared to responders (p < 0.001). Detailed clinical characteristics of respondents with the affiliated DrHy-Q scores are depicted in table 1.

DrHy-Q scores

The DrHy-Q score in our study population was median 11.7 (min - max: 0 - 88.3). The DrHy-Q scores obtained in the Italian and Turkish populations were: median 36.0 (0 - 73.0) and 32.5 (2.6 - 56.2), respectively. Overview of the demographic and drug hypersensitivity characteristics of the three study populations are clearly depicted in table 3.

Outcome validation variables

The rates of missing values for the individual items of the DrHy-Q were consistently low, ranging from 0% to 1.6%, and occurred missing at random. The construct validity was good: CFI 0.992, TLI 0.991 and RMSEA 0.064. The correlation between the DrHy-Q total scores and the RAND-36 domain scores was moderate as expected (table 2), representing acceptable divergent validity. The discriminant ability of the DrHy-Q was confirmed for patients with one vs. two or more drug hypersensitivities (median, [min-max]: 8.33, [0 - 88.3] vs. 18.33, [0 - 83.3], p = 0.001), indicating more impairment in HRQoL in patients with two or more hypersensitivities. No significant differences were detected between severity of HDR symptoms, implicated drug or reaction type (table 2). The internal consistency was high, with a Cronbach’s alfa of 0.944. The test-retest was assessed in 91 responders (65.9% female, mean age 57.5 ± 13.9 years). The ICC for test-retest reliability was 0.950 (p = 0.0001), indicating excellent reliability.

Discussion

In this study, we have showed that the Dutch DrHy-Q is a valid and reliable tool for assessing quality of life in patients with drug hypersensitivity.

Our findings are in line with previous validation passages of the questionnaire for the Italian and Turkish populations in terms of validation outcomes (6,7). The Dutch DrHy-Q proved the 1-dimensional structure of the original Italian questionnaire, as previously confirmed by the Turkish DrHy-Q (7). The low negative correlations with the RAND-36 domains suggest that the Dutch DrHy-Q is able to capture specific aspects of patient experiences that are barely detectable with a generic tool. This is also in concordance with the findings of the Italian (6) and Turkish (7) DrHy-Q, since both versions showed correlation with the Psychological General Wellbeing Index domains (22), a similar generic HRQoL tool, varying between [min - max] rho 0.002 - 0.143 (p = 0.001) and rho = -0.254 - -0.378, respectively (p = 0.001). The Dutch DrHy-Q was able to discriminate between patients with one or more than one implicated drug hypersensitivity reaction. In the Turkish study, a discriminative ability with respect to the presence of respiratory symptoms was also observed (7), but is not confirmed in our study. The discriminative ability between severity of reactions (anaphylactic shock vs. other reactions) reported in the Italian validation (6), could also not be seen in our study. A recent additional Italian study (n = 65) showed signifi-
Assessment of validity and reliability of Drug Hypersensitivity Quality of Life Questionnaire: The Dutch experience

In this study we also observed a country specific difference in total DrHy-Q scores. We found a considerably lower median DrHy-Q score in our population compared to the Italian and Turkish populations, with scores of 36 and 32.5, respectively (6,7). This observed difference in DrHy-Q values could be attributed by several contributing factors. First, the investigated populations showed several differences leading to lower comparability. Participants of our study had completed their diagnostic work-up and counseling before study inclusion compared to the possible heterogeneous group in the other countries. Since it is shown that the DrHy score is sensitive to diagnostic interventions (pre-intervention score 33 vs. post-intervention score 29; p = 0.008) in the Turkish population (7), this could explain the lower DrHy-Q value to some extent. Furthermore, participants of this study were of higher age compared to those in the other populations and had more comorbid diseases, both variables which are known to influence generic HRQoL tools (15). Within our study, only the impact of comorbid disease on DrHy-Q was observed.

Differences in drug consumption between countries also might cause the difference in DrHy-Q scores and is illustrated by the antibiotic Defined Daily Dose (DDD) consumption between the three countries. As antibiotics account for the majority of drug hypersensitivities (2) the antibiotic Defined Daily Dose (DDD) consumption between the three countries was compared. Recent reports showed an antibiotic use of 9.4 DDD per 1000 inhabitants per day in the Netherlands versus 13.9 - 16.7 DDD per 1000 inhabitants per day in Italy and 42.3 DDD per 1000 inhabitants per day in Turkey in the past several years (24,25). This higher intention of drug consumption might increase the perception of impairment in patients with (antibiotic) drug hypersensitivities and thus differences in DrHy-Q scores. Finally, also social and cultural differences could influence HRQoL perception and

Table 3 - Study population characteristics and DrHy-Q scores obtained in across countries.

<table>
<thead>
<tr>
<th></th>
<th>The Netherlands</th>
<th>Italy</th>
<th>Turkey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>124</td>
<td>365</td>
<td>711</td>
</tr>
<tr>
<td>DrHy-Q score, median (min - max)</td>
<td>12 (0 - 88)</td>
<td>36 (0 - 73)</td>
<td>33 (3 - 56)</td>
</tr>
<tr>
<td>Age in years, median (min - max)</td>
<td>58 (19 - 87)</td>
<td>46 (18-79)</td>
<td>42 (18 - 78)</td>
</tr>
<tr>
<td>Gender, female %</td>
<td>65.3</td>
<td>67.5</td>
<td>73.6</td>
</tr>
<tr>
<td><strong>Education, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>4.1</td>
<td>4.0</td>
<td>33.1</td>
</tr>
<tr>
<td>High school</td>
<td>64.5</td>
<td>59.0</td>
<td>38.8</td>
</tr>
<tr>
<td>University</td>
<td>31.4</td>
<td>37.0</td>
<td>28.1</td>
</tr>
<tr>
<td>Concomitant comorbid disease, %</td>
<td>65.3</td>
<td>41</td>
<td>36.5</td>
</tr>
<tr>
<td><strong>Number of implicated drug, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>65.3</td>
<td>67.2</td>
<td>44.3</td>
</tr>
<tr>
<td>≥ 2</td>
<td>26.7</td>
<td>32.8</td>
<td>53.0</td>
</tr>
<tr>
<td><strong>Implicated drugs, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>50.0</td>
<td>53.2</td>
<td>38.7</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>11.3</td>
<td>21.8</td>
<td>65.9</td>
</tr>
<tr>
<td>Others</td>
<td>39.5</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td><strong>Type of symptoms of the drug hypersensitivity reaction, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin / Angioedema</td>
<td>86.3</td>
<td>73.4</td>
<td>75.0</td>
</tr>
<tr>
<td>Respiratory / Cardiovascular</td>
<td>48.4</td>
<td>26.6</td>
<td>46.4</td>
</tr>
</tbody>
</table>

DrHy-Q: Drug Hypersensitivity Quality of Life Questionnaire; n: Number
could explain a lower DrHy-Q score. This assumption is already established in different validated HRQoL questionnaires for use in allergic diseases, such as asthma (26) and food allergy (27), in which Dutch participants show a favorable health perception compared to other populations.

Our study has some limitations. The small sample size and tertiary setting compromises the value of this dataset for establishing DrHy-Q norm scores for the general Dutch population and for different age and gender strata. The frequency of patients diagnosed with a NSAID drug hypersensitivity was low in this study population compared previously published analyzed population. Since many patients have been referred by other departments from our tertiary university hospital, reference bias could explain the relative low frequency of NSAID hypersensitivities compared to particularly antibiotic hypersensitivities. Ethnic differences in the population were not assessed, as well as the responsiveness of the Dutch DrHy-Q in diagnostic interventions. Both topics are of interest for further research. For future studies, a multi-center design and larger sample sizes in comparable population are needed to investigate cross country comparability. In addition, further studies are needed to explain country specific differences in drug hypersensitivity related quality of life as this study only described a qualitative analysis since statistical comparison was not possible. In conclusion, the Dutch version of the DrHy-Q has shown to be a practical, reliable, and valid instrument for evaluation of drug hypersensitivity related quality of life in the Netherlands.

References

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Successful of subcutaneous and oral hyposensitizing therapy in 30 patients

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²Faculty of Medicine, University of Towson, Maryland, USA
³Department of Dermatology, University of Modena and Reggio Emilia, Modena, Italy
⁴Studies Doctors Gathered Director, Italy

Summary

Background. Pharmacotherapy and immunotherapy are the main treatment modalities for respiratory allergy. The aim of this paper has been to evaluate the efficacy and tolerability of subcutaneous and sublingual immunotherapy in association in allergic patients, and to demonstrate that the patients who have performed a second oral vaccination cycle after 4-5 years from the first subcutaneous treatment, derive benefits that may last for years. This is due to immune system's plasticity. Methods. The study was conducted in 30 allergic patients which had previously executed a full cycle of classical subcutaneous immunotherapy, with a partial remission of symptoms. After 4-5 years, they were subjected to sublingual immunotherapy for the same allergen, improving the results obtained. Results. All the patients reported a decrease or absence of clinical symptoms, a reduction in the use of anti-allergic drugs, and lower values of PRIST and RAST after the treatment. Conclusions. The results of this clinical study confirm the improvement of results when subcutaneous and sublingual immunotherapy are associated.

Key words

immune response; immunotherapy; sublingual immunotherapy (SLIT); T cell; vaccination

Introduction

Respiratory allergy occurs in more than 500 million persons around the world. In developed countries, allergic rhinitis affects between 10 and 25% of the general population, with an average of 23% in European countries. The risk of asthma is higher in patients with rhinitis. Allergies to grass, weed and tree pollen characteristically result in seasonal rhinitis symptoms, which correlate with the presence of allergen exposure in the environment. The primary approach to the control of the symptoms is the identification and avoidance of the causal allergens, which is often impossible for pollen. Pharmacotherapy and immunotherapy are the main treatment modalities. In contrast with pharmacotherapy, allergen injection immunotherapy has long term benefits that may persist for at least 3 to 5 years after discontinuation. These include long term remission of symptoms, a decrease in the onset of new sensitizations and, in subjects with rhinitis alone, a reduction in the likelihood of progression of their disease from rhinitis to asthma. Despite the proven efficacy to the traditional approach, there are clear limitations. These limitations lead physicians to research alternative routes of administration of immunotherapy, such as the sublingual route, or to search for molecules, such as novel adjuvants, modified natural allergens, peptide immunotherapy, recombinant allergens and their hypoallergenic variants, that will be dependent on the outcome of focused, adequately powered, and well designed clinical trials.

In this clinical study we resume the history of 30 patients, administered with a three-years classical subcutaneous immunotherapy with a partial remission of symptoms, in which the use of three-years sublingual immunotherapy for the same allergen, improved the results obtained.
Concerning the case of pollen with seasonal flowering, the drug of the maintenance phase was administered in cycles over three years and interrupted only during the period of pollination. During treatment, the patients were subjected to clinical control once a month, monitoring and checking the tolerability of the vaccine and the symptoms. At the end of the maintenance phase we carried out a follow-up at time zero, one month, three months and six months later. After twelve months, we repeated the Prick test.

Results

All the 30 patients treated reported a benefit with reduction of 80% in respiratory symptoms, complete absence of asthma in patients with allergy to dermatophagoides, and reduction in the use of anti-allergic drugs (in all treated patients the corticosteroids therapy was no longer necessary and antihistamines just in case of need in heyday). Respiratory symptoms were evaluated on the basis of:

1. The presence of cough, rhinitis and conjunctivitis;
2. An otolaryngologist examination that verified the presence of a hyperemic mucosa on allergic basis without other deficits (ex. Nasal septum deviation);
3. Administration of RQLQ (Rhinoconjunctivitis Quality of life questionnaire).

The ocular symptoms were evaluated on the basis of an ophthalmic examination, which verified the presence of a hyperemic conjunctiva on allergic basis.

The RAST, performed after the vaccine, had a lower value than that before treatment, showing only a weak positivity (table 2). Comparing the prick tests, we have ascertained that the patients with a prick test 3 + before the treatment presented 2 + after

Materials and methods

In our study we enrolled 30 patients of both sexes and aged between 30 and 60 years, with chronic and/or seasonal inhalatory allergy, and who had already executed a full cycle of subcutaneous hyposensitizing therapy 4-5 years before. The patients were divided according to the allergy’s type and symptoms (table 1). For each patient, after the signature of informed consent, PRIST, RAST and PRICK TEST for inhalants were performed, with similar results to those observed before hyposensitizing therapy. We therefore started a new treatment with oral hyposensitizing therapy, that comprises an induction and a maintenance phase. In the induction phase, lasting 13 days, for each patient 6 bottles of 4 ml each were used, with increasing concentrations of the allergen, administered by drops in the following way:

- First bottle: 2 drops on first day, 4 drops on second day, 6 drops on third day, 8 drops on fourth day, 10 drops on fifth day, 12 drops on sixth day, 14 drops on seventh day, 16 drops on eighth day;
- The remaining five bottles: 1 drop on ninth day, 2 drops on tenth day, 3 drops on eleventh day, 4 drops on twelfth day, 5 drops on thirteenth day.

On the fifteenth day, the maintenance phase begins, where patients continue therapy with three drops per week for three years, using the third bottle, with the highest concentration of allergen. All patients were subjected to this stage, even those with sensitization to perennial allergens. In this study, we used a sublingual immunotherapy produced by Lofarma, an Italian pharmaceutical company.

Regarding the cases of allergy to Dermatophagoides, the maintenance phase consisted in the daily administration of the drug for three years.

Table 1 - Distribution of patients according to the allergens and symptoms.

<table>
<thead>
<tr>
<th>Allergens</th>
<th>No. patients</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grasses mix</td>
<td>10</td>
<td>Rhinitis, cough, conjunctivitis</td>
</tr>
<tr>
<td>Pellitory mix</td>
<td>10</td>
<td>Rhinitis, cough, conjunctivitis</td>
</tr>
<tr>
<td>Dermathophagoides mix</td>
<td>10</td>
<td>Rhinitis, cough, conjunctivitis, asthma</td>
</tr>
</tbody>
</table>

Table 2 - Comparing the RAST before and after the treatment.

<table>
<thead>
<tr>
<th>Allergens</th>
<th>RAST before the treatment</th>
<th>RAST after the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grasses mix</td>
<td>300 iu</td>
<td>250 iu</td>
</tr>
<tr>
<td>Pellitory mix</td>
<td>350 iu</td>
<td>150 iu</td>
</tr>
<tr>
<td>Dermatophagoides mix</td>
<td>600 iu</td>
<td>200 iu</td>
</tr>
</tbody>
</table>
Successful of subcutaneous and oral hyposensitizing therapy in 30 patients

the vaccine, and the ones who at the first had a positivity 2+ became 1+ after the therapy.

Discussion

In atopic allergy, type 2 helper T lymphocytes (Th2 cells) are elevated in relation to regulatory T lymphocytes (Treg cells). In healthy subjects the ratio is vice versa. It seems that tolerance generated through allergen-specific Treg cells is the immunologic reaction mode towards allergens in healthy non-atopic subjects. It has been found that hyposensitization will correct the imbalance of Th2 and Treg cells and restore the normal immune response to allergens.

Our results demonstrate the enormous effectiveness of oral immunotherapy, performed after one subcutaneous. In fact, the patients who have performed a second oral vaccination cycle 4-5 years after the first subcutaneous treatment, derive benefits that last for years after suspension of the therapy. Six years have passed from the administration of second oral vaccine, and therefore we can say that these patients present a stable and unaltered condition, until now. Those who have been subjected only to the first vaccination cycle, have showed an improvement in symptoms until 3 years after suspension the therapy. To explain how this is possible, we must refer to the concept of “biological plasticity”, that is the ability to change in response to external stimuli and then to show memory. The biological plasticity is a form of adaptation that reflects the evolution of each individual, and therefore explains why different organisms may respond to the same stimulus in different ways. The same thing happens in allergy sufferer undergoing vaccine, which will induce changes, such as the generation of antibody heritage. The Immune System maintains the memory of those systems that have been shown effective in thwarting previous attacks. Therefore, when the allergic subject is subjected to the second vaccination cycle after many years, you get a much greater benefit due to the fact that the repetition of the cycles of immunotherapy potentiates the effect of the first treatment, thus allowing to maintain the immune memory of these patients; it has a synergistic action between the two treatments, made possible precisely by the memory of the first.

Conclusions

The efficacy of allergen injection immunotherapy for allergic respiratory disease has been confirmed in systematic reviews and meta-analyses for asthma and for allergic rhinitis. The sublingual route is usually considered as an alternative to subcutaneous immunotherapy. Instead, we demonstrated that the subcutaneous and oral immunotherapy in association represents a safe and effective treatment. Considering the success of 100% obtained in our study, it symbolizes a revolution in the field of prevention, above all for patients with atopy to perennial allergens suffering serious trouble all year.

References

Eosinophil fungal rhinosinusitis caused by Fusarium infection secondary to odontogenic maxillary sinus disease: when collaboration between otolaryngologist and allergologist leads to the correct diagnosis and therapy

P. Gamba¹, C. Lombardi²

Introduction

Chronic rhinosinusitis with (CRSwNP) and without nasal polyps (CRSsNP) in its many forms, constitutes one of the commonest conditions encountered in medicine and may present to a wide range of clinicians from primary care to accident and emergency, pulmonologists, allergists, otorhinolaryngologists and even intensivists and neurosurgeons when severe complications occur (1,2). Odontogenic rhinosinusitis is a relevant infectious condition of the paranasal sinuses. Approximately 5-15% of the population suffers from chronic rhinosinusitis, and in 10-12% of them, it is of dental origin (3). The widespread use of dental implants and reconstructive procedures for dental implant placement has led to new types of complication as a chronic eosinophilic rhinosinusitis secondary to Fusarium infection in the maxillary sinus. The patient was initially evaluated by the allergologist, and subsequently successfully treated by the otolaryngologist with Functional Endoscopic Sinus Surgery. The advantages of endoscopic sinus surgery include more accurate visualization, no external incision, reduced soft tissue dissection, and reduced hospital stay. Chronic maxillary sinusitis of dental origin is a common disease that requires treatment of the sinusitis as well as of the odontogenic source.
more accurate visualization, no external incision, reduced soft tissue dissection, and reduced hospital stay. Chronic maxillary sinusitis of dental origin is a common disease that requires treatment of the sinusitis as well as of the odontogenic source. Dental Implantation can occasionally be compromised by anatomical limitations, as well as by the status of alveolar bone and surrounding soft tissue. Implantation around the posterior maxilla area is often challenging because of alveolar bone resorption, sinus pneumatization or other reasons. Therefore, implants should be treated constantly after surgery. Improving the success rate of implant placement in the molar area requires an accurate functional and anatomical understanding of the maxillary molar area, as well as of potential complications that may arise during and after surgery and their appropriate management (6).

Case Report

A 55-year-old, Caucasian, male patient was sent for evaluation to our ENT department after a previous allergologic evaluation, that had excluded an allergic cause of the chronic rhinosinusal symptoms. The patient reported a considerable pain in the left zygomatic area with headache in the left temporal region. The patient had a history of dental extraction of the number 26, and underwent single dental implant installation. Medical therapy was administered, including empirical antibiotics (penicillin, clindamycin), non-steroidal anti-inflammatory drugs, expectorants and antihistamines, which were prescribed to mitigate symptoms; however, the patient showed no improvement after 4 weeks of follow-up, and the persistence of signs and symptoms of discomfort indicated that further investigation was needed. Panoramic view revealed that the single implant was protruding into the left maxillary sinus, and that the radiopacity of the sinus was increased (figure 1). Coronal view computed tomography (CT) revealed definite signs of sinusitis, with opacification of the left maxillary sinus as well as ethmoidal sinus, and confirmed that

Figure 1 - Panoramic view, left maxilla sinus bone grafting and #26 implantation revealed dental implant protrusion into the left maxillary sinus.

Figure 2 - Paranasal sinuses computed tomography revealed mucosal thickening and opacification with air bubbles in the left maxillary sinus and the presence of “high and low density areas” material into the sinus with a central gutta-percha pin. Coronal CT images revealed radiopaque concretion in the left maxillary sinus in a typical mycosis, in this case Eosinophil Fungal Rhinosinusitis type Fusarium.

Figure 3 - MRI, axial T2-weighted image demonstrates a fluid level with high signal level with high signal posteriorly.
In many cases of maxillary sinusitis, dysfunction of mucociliary clearance is a major clinical problem. The stagnation of secretions and obstruction of excretion from and ventilation of the sinus is a common issue. In the case presented, a dental implant was protruding approximately 5 mm into the sinus (figure 2). MRI, axial T2-weighted image demonstrated a fluid level with high signal level with high signal posteriorly (figure 3). Based on this evidence of obstruction of the ostium of the left nasal cavity and infection of the mucocele of the left maxillary sinus, we consulted an Oral-Maxillofacial surgeon and concluded that an intranasal approach alone would be sufficient to remove the mucocele, and FESS was performed. The middle turbinate was widely excised so that pus and infected bone graft particle could be flushed from the sinus cavity. The ostium was exposed by removal of the uncinated process on the middle meatus to access to ostium and the ethmoidal sinus. Edematous, hyperplastic nasal mucosa within the sinus was enucleated after the natural ostium was surgically enlarged (figure 4) then the sinus was irrigated with normal saline until no additional free-floating particles were observed. During this procedure, the dental implant was not removed because of nasal discharge stopping and increased radiopacity. The implant was left stable. The patient received absorbent nasal packing for 2 days, no complications occurred and symptoms improved gradually over the healing period. The patient was followed up for 5 weeks at the ENT Department, with progressive improvement (figure 5). Histological examination revealed typical fungal masses, an eosinophil fungal rhinosinusitis type Fusarium, on injured mucosa and on crystallization cores with a central gutta-percha pin (Grocott) (figure 6). The patient’s immunological profile study did not document a condition of immunodeficiency (which occurs in many patients with infection by Fusarium).

**Figure 4** - Endoscopic view, left maxillary sinus, the fungal concretion is recognizable. Further purulent secretion with fungal spores is evacuated through the natural ostium.

**Figure 5** - Endoscopic view: condition 2 months after functional endoscopic sinus surgery (FESS), after uncinectomy and maxillary sinus ostium enlargement. After aspiration of thickened pus the base of the left maxillary sinus was found, reaching freely into the lumen.

**Figure 6** - Histological examination revealed typical fungal masses, an eosinophil fungal rhinosinusitis type Fusarium, on injured mucosa and on crystallization cores with a central gutta-percha pin (Grocott).

**Discussion**

In many cases of maxillary sinusitis, dysfunction of mucociliary clearance is a major clinical problem. The stagnation of secretions and obstruction of excretion from and ventilation...
within the maxillary sinus are predisposing factors for sinus infection. The area between middle turbinate and lateral nasal wall often has an anatomical variation; therefore, edema of the mucosa can result in obstruction of the ostium and dysfunction of mucociliary. Maxillary sinus floor lift has been reported to cause postoperative sinusitis. The elevation of the Schneiderian membrane could affect a sinus homeostasis and lead to sinusitis by temporal obstruction of a physiological sinus drainage through the osteomeatal unit. Mucosal inflammation caused by misplaced implant can similarly cause mucosal inflammation and stenosis of the osteomeatal unit with detrimental effect on sinus ventilation. Recommended treatment for dental implant-related sinusitis typically involves surgical restoration for proper drainage and ventilation of the sinus, interrupting the described sequence of events that lead to sinus infection. FESS is a relatively recent surgical procedure used in the treatment of maxillary sinusitis (7,8). Simple elimination of the irritating stimulus, such as exposed or displaced implant, could also be considered. Reported in the literature indicated that implant exposure greater than 4 mm from the sinus floor can give rise to sinusitis or rhinosinusitis. In this report the implant fixture was not removed due to not only the exposed length (4 mm), but also the significant stability. In the posterior molar region, where implant placement is difficult, many complication of maxillary sinus sequent implant placement can occur. The symptoms of acute maxillary sinusitis include discomfort or pain in the facial area and nasal discharge (9). Chronic maxillary sinusitis arises from obstruction of the ostium of the paranasal sinus. There is destruction of the epithelium, with progressive infection that leads to irreversible changes. The maxillary ostium is located close to the maxillary roof, and the maxillary sinus floor is located about 0.5 cm below the nasal floor. The consequent welling of the maxillary mucosa makes paranasal ostium drainage difficult. Occlusion of the osteomeatal unit can reduce the drainage of discharge and the ventilation of the paranasal cavity whereby inducing paranasal sinusitis. When the inside of the maxilla is overfilled with bone graft materials, it can induce necrosis of the maxillary cavity (10). In addition, the loss of bone materials within the maxillary cavity can lead to maxillary sinusitis. Perforation of the maxillary sinus membrane during dental implant placement can also induce maxillary sinusitis. Perforation of the maxillary sinus membrane can allow the graft material, particularly synthetic bone powder, to escape from the maxillary sinus through the nose, and also it impedes the mucociliary action of the maxillary sinus membrane and leads to infection (11,12). The most common form of mycoses is the non-invasive, saprophytic maxillary sinus mycoses (13). In the present case, histological examination revealed an eosinophil fungal rhinosinusitis type Fusarium, on injured mucosa and on crystallization cores that fill a maxillary sinus, but are only invasive in the rarest cases. They require thorough surgical removal, whereby attention must be paid to good ventilation of the affected paranasal sinus (14). In this case of the maxillary sinus, the mass can be removed thorough functional endoscopic sinus surgery, after suitable widening of the natural ostium. It is important to get a good overview of the maxillary sinus, e.g. with a 70° telescope. Relapses after mycoses almost always represent re-infection caused by fungal material left behind (15). Fusarium species cause a broad spectrum of infections in humans, including superficial infections such as keratitis and onychomycosis, as well as locally invasive and disseminated infections (16). Invasive and disseminated infections occur almost exclusively in severely immunocompromised patients, particularly among those with prolonged and profound neutropenia and/or severe T cell immunodeficiency. Among patients with hematologic malignancy, the infection predominates during periods of neutropenia, typically among patients with leukemia receiving induction chemotherapy. Fusarium species may also cause allergic diseases, such as sinusitis in immunocompetent individuals (17), and mycotoxicosis following ingestion of food contaminated by toxin-producing Fusarium species (18). Odontogenic sinusitis is a well-recognized, but understudied form of sinusitis. Odontogenic sinusitis requires unique diagnostic criteria and a treatment regimen that differs from non-odontogenic sinusitis. Odontogenic sinusitis is often misdiagnosed (19). Radiology reports commonly do not mention dental pathology (20). Management of odontogenic sinusitis needs to be tailored to each patient and many complex interplay specialist competencies involving medical management, dental surgery, and functional endoscopic sinus surgery (21).

References


Disappearance of severe oral allergy syndrome following omalizumab treatment

Ambulatorio di Allergologia, Clinica San Carlo, Paderno Dugnano, Italy

Key words
food allergy; IgE; omalizumab; oral allergy syndrome; treatment

Summary
The first case of disappearance of apple-induced oral allergy syndrome in a birch pollen-allergic patient following omalizumab treatment is reported. This observation in a case of type 2 food allergy suggests that omalizumab is potentially an effective preventive treatment for patients with severe, type 1 food allergies.

Introduction
It has long been known that birch pollen-allergic patients frequently develop oral itching with angioedema of the lips following the ingestion of fresh foods and vegetables, due to the presence of allergen proteins homologous to the major birch pollen allergen, Bet v 1. This phenomenon is known as oral allergy syndrome (OAS). Although in most cases limited to the oral cavity, reactions may be sometimes severe enough to involve the pharynx and to prevent patients to eat a large spectrum of fresh and raw fruits and vegetables, with a significant reduction of their quality of life. The apple is the fruit most frequently involved in such food allergies, due to the very high homology of its PR-10 allergen, Mal d 1, with Bet v 1 (1-4). Previous studies showed that allergen immunotherapy with birch pollen extracts may reduce or abolish secondary apple allergy (revised in [5]).

Omalizumab, a humanized anti-IgE monoclonal antibody indicated for a long time in severe cases of allergic asthma, has been recently introduced also as a treatment for patients with refractory chronic urticaria. Omalizumab binds the Fc3 subunit of free IgE molecules and it is generally accepted that the reduced binding of free specific IgE to the high affinity IgE receptor (FceRI) eventually leads to a reduced density of specific IgE on the surface of mast cells and basophils, and to the down-regulation of the receptor itself. In food allergy, omalizumab has been experimentally tried in cases of severe allergies both as a monotherapy (mainly in adults) (6-8) and as an add-on treatment to oral immunotherapy (OIT; virtually only in children) (9-12). In most cases, the drug was able to increase significantly the threshold dose of offending foods required to induce adverse reactions. No data about the effect of omalizumab in type 2 food allergies are available to date.


Case report

A 51-year old woman was seen at the allergy department of the Clinica San Carlo. She had suffered from severe generalized pruritus for more than 1 year, sometimes associated with the occurrence of itchy wheals. The skin complaints progressively worsened, with the occurrence of recurrent large wheals that no longer responded to second generation antihistamines, even at higher than licensed doses (levocetirizine 15 mg/day). At this time point, the Urticaria Activity Score (UAS-7) scored 32. The patient also had a 20-year history of seasonal springtime rhinoconjunctivitis, and reported severe OAS following the ingestion of Rosaceae (apple, peach, cherry, apricot, plum and almond), grapes, fennel, carrot, and kiwi. The ingestion of these fruits caused severe oral itching and tingling, and the rapid onset of angioedema of the lips and eyelids. The woman reported that the apple was by far the plant-derived food inducing the most severe reactions. The patient underwent skin prick tests (SPT) with a large series of commercial extracts of airborne allergens (Allergopharma, Reinbeck, Germany) including pollens (grass, mugwort, ragweed, pelletaria, plantain, birch, cypress and olive), house dust mites, Alternaria spp, and dog and cat dander. Birch and cypress pollen scored strongly positive (mean wheal diameter 12 mm), as did a SPT with fresh Golden Delicious apple by the Prick-Prick technique (10 mm). Both a SPT with commercial date palm, profilin-enriched, pollen extract (ALK-Abellò, Hørsholm, Denmark; 50 μg protein/ml) and a SPT with a commercial peach extract (ALK-Abellò; containing LTP 30 μg/ml), markers of profilin and lipid transfer protein hypersensitivity, respectively, scored negative. The level of specific IgE to birch pollen, measured by ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden), was 12.6 kUA/L. Chronic spontaneous urticaria (CSU), resistant to antihistamines, was diagnosed, along with birch and cypress pollinosis and type 2, cross-reactive food allergy. In view of the severity of the CSU, after written informed consent was obtained from the patient, subcutaneous omalizumab 300 mg/month was started. Urticaria promptly and completely responded as short as 1 week after the first administration, and at month 3 of treatment, during the birch pollen season, an open challenge with a Golden Delicious apple was carried out. The woman was able to tolerate an entire apple without symptoms. At this point SPT with birch pollen extract and fresh Golden delicious apple were performed. While the former induced a wheal whose mean diameter was similar to that observed at the first visit (12 mm), the apple-induced wheal was much reduced (mean diameter 4 mm).

Conclusion

This is probably the first report on the effects of anti-IgE treatment on type 2 food allergy. It confirms the conclusions of studies on type 1 food allergies that omalizumab markedly increases the threshold dose of food allergen needed to elicit clinical symptoms. Looking at studies on chronic urticaria and bronchial asthma showing that the effect of the drug is short-lived, one can expect that the effect of omalizumab on food allergy vanishes in as short as two months once the drug is discontinued. Nonetheless, omalizumab seems to represent an effective preventive treatment for patients with severe food allergies.

References