edra | Issn 1764-1489 | Volume 53 N. 6/2021 – November 2021

European Annals of Allergy and Clinical Immunology

THE OFFICIAL JOURNAL OF AAIITO | ASSOCIAZIONE ALLERGOLOGI IMMUNOLOGI ITALIANI TERRITORIALI E OSPEDALIERI
THE OFFICIAL JOURNAL OF SPAIC | SOCIEDADE PORTUGUESA DE ALERGOLOGIA E IMUNOLOGIA CLINICA

6/2021

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European Annals of Allergy and Clinical Immunology

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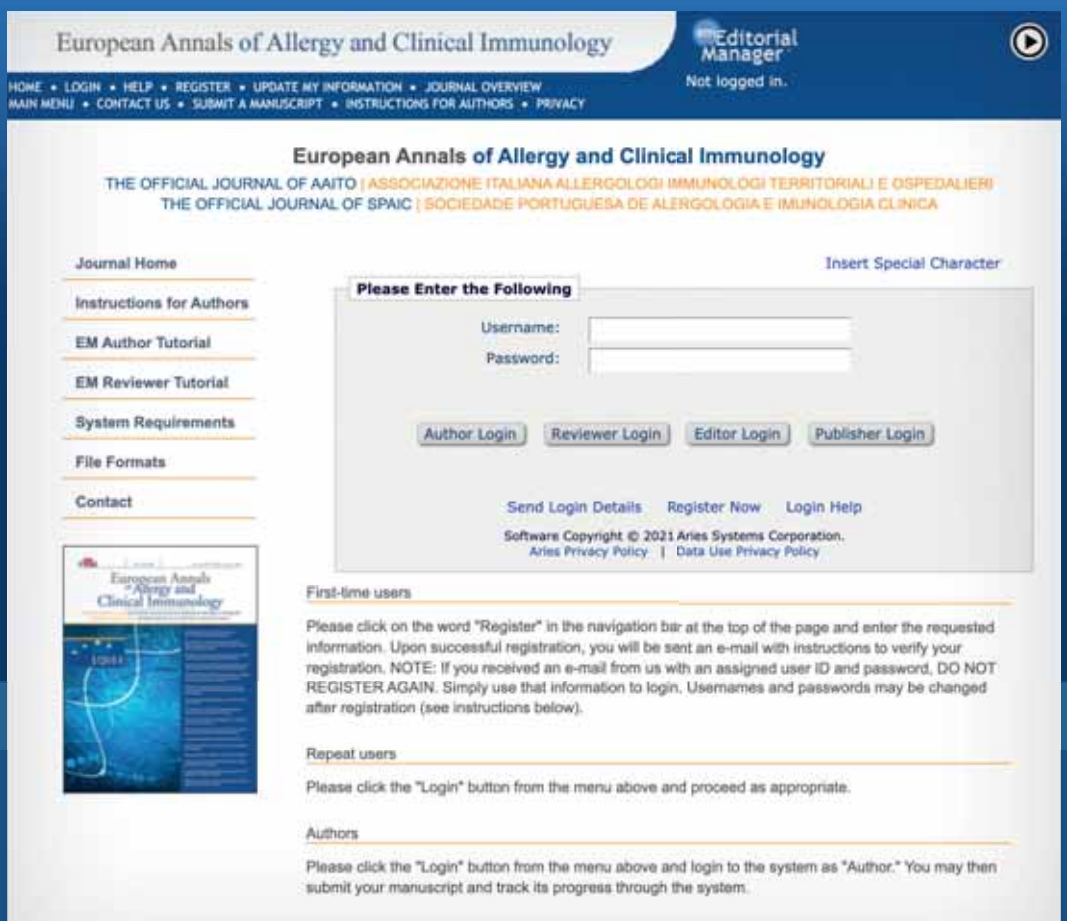

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Printing

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"European Annals of Allergy and Clinical Immunology" registered at Tribunale di Milano - n. 336 on 22.10.2014

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Allergic rhinitis: impact on quality of life of adolescents

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Key words
Allergic rhinitis; quality of life; adolescents; rhinoconjunctivitis; allergy.

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Doi
10.23822/EurAnnACI.1764-1489.176

Summary
Adolescence is one of the most rapid phases of human development, in which biological maturity precedes psychosocial maturity. Rhinoconjunctivitis (ARC) is present in around 15% of 13-14-year-old children, which indicates a higher prevalence when compared with 6-7-year-old children (8.5%). During childhood (0-10 years) prevalence of allergic rhinitis (AR) is higher among males compared to females. Quite the reverse, during adolescence (11-17 years) females display higher prevalence of AR compared to males. However, when they reach adulthood (18-79 years), there is no difference in prevalence between genders. AR and ARC have significant physical and mental impacts on the QoL of adolescents and their parents. Apart from the adverse effects of first generation antihistamines, which include sedating effects, AR/ARC leads to school absences and poorer performance due to distraction, fatigue and irritability. The mobile technology facilitates an innovative investigatory approach to better and more precisely characterize allergy symptoms and their association with other allergic diseases. The success of treatment lies in the partnership between adolescents with AR and mobile technology, allowing them to have more information both on the disease and treatment. Adolescence is a special period in which AR is highly prevalent with some sex-dependent differences. There are also peculiarities on how AR affects QoL of adolescent patients.

Impact statement
AR and ARC have significant physical and mental impacts on the QoL of adolescents and their parents.

Introduction

The World Health Organization (WHO) describes adolescence as one of the most rapid phases of human development, in which biological maturity precedes psychosocial maturity. It is worth noting that the changes occurring in adolescence have health consequences not only in adolescence but also over the life-course, and therefore, explicit and specific attention in health policy programs should be paid during this period of life (1).

Objective

Chronic disease such as allergic rhinitis affects health related quality of life (HRQoL) of children going through the process of growth and development by substantially interrupting their daily activities. The symptoms of allergic rhinitis can cause sleep disturbance, fatigue, poor concentration, and limitations in daily activities. This review aims to evaluate the literature regarding the burden of allergic rhinitis (AR) and allergic rhinoconjunc-

tivitis (ARC) in adolescents (aged 10-19 years) and provide to healthcare professionals with an understanding of the impact of Allergic Rhinitis in adolescents.

Methods

Data source

The generic terms "rhinitis", "adolescents" and "quality of life" have been screened using PubMed platform.

Data synthesis

Health Related Quality of Life (HRQoL)

A critical aspect in the management of respiratory allergy is its burden on patient's health-related quality of life (HRQoL), defined as the impact of a disease and its treatment perceived by patients themselves (2).

Health-related quality of life (HRQoL) is an individual's or a group's perceived physical and mental health over time (3). It is usually assessed via multiple indicators of self-perceived health status and physical and emotional functioning. Together, these measures provide a comprehensive assessment of the burden of preventable diseases, injuries, and disabilities (4).

The use of questionnaires to assess HRQoL is today recommended by international guidelines and regulatory authorities for the evaluation of new drugs. Furthermore, the fundamental role of patient's perspectives is underlined by the GRADE system, which represents the best option in defining the criteria for grading evidence and developing guidelines. The RHINASTHMA-Adolescents questionnaire is able to discriminate the disease severity level, it is sensitive for individual changes, and it is simple to administer, giving an immediate idea of the burden of the disease in patient's everyday life (2). AR causes a global negative impact on the HRQL of children and teenagers, altering mostly the physical function, according to the perception of parents or guardians, and affects negatively the family group (5).

Results

Prevalence of allergic rhinitis in adolescence

The ISAAC (The International Study of Asthma and Allergies in Childhood) Phase III study has analyzed the prevalence and severity of current symptoms of asthma, rhinoconjunctivitis and eczema in the main regions of the world in approximately 1,200,000 children. The results of the epidemiological survey showed that rhinoconjunctivitis was present in around 15% of 13-14-year-old children, which indicates a higher prevalence when compared with 6-7-year-old children (8.5%) (6).

Allergic rhinitis (AR) in children has some peculiarities. Even though nasal congestion is the main symptom in adolescents (7) halitosis deserves special attention due to the social impact that it can have in their lives.

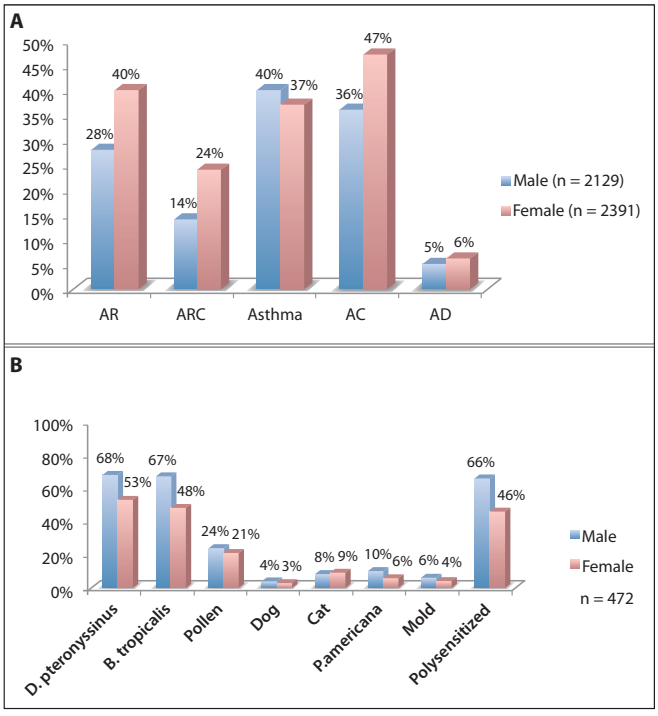
Comorbidities may facilitate the diagnosis of AR, such as asthma, eczema, pollen-food syndrome, sleep disorders and hearing impairment. Other conditions may lead to non-allergic non-infectious rhinitis diagnosis: esophageal reflux, hormonal dysfunction, exposure to irritants or specific drugs (8).

Sex differences in allergy

During childhood (0-10 years) prevalence of AR is higher among males compared to females. On the contrary, during adolescence (11-17 years) females display higher prevalence of AR compared to their male counterparts. However, when they reach adulthood (18-79 years), there is no difference in prevalence between genders. The same pattern occurs, even more pronounced, for prevalence of coexisting AR and asthma (9). Allergic rhinitis in obese teenage girls may be a risk factor for wheezing (10).

A recent analysis performed in 4,500 children aged 13-14 years has shown that females not only have a higher prevalence of AR compared to males, but also of allergic rhinoconjunctivitis (ARC), asthma, allergic conjunctivitis (AC) and atopic dermatitis (AD) (**figure 1 A**). Interestingly, there is an opposite allergic sensitization pattern with respect to gender, with more allergic

Figure 1 *- (**A**) Prevalence of allergic diseases according to gender (n = 4,520). (**B**) Allergic sensitization pattern according to gender (n = 472).*



AR: allergic rhinitis; ARC: allergic rhinoconjunctivitis; AC: allergic conjunctivitis; AD: atopic dermatitis. Adapted from reference 11 with permission.

sensitization in boys than in girls (**figure 1 B**). Moreover, it has also been observed that monosensitization is more frequent in females, while polysensitization is more common in males (11).

Approaching the patient

Effect of allergic rhinitis on Health Related Quality of Life (HRQoL)

AR and ARC have significant physical and mental impacts on the HRQoL of adolescents (12). Apart from the adverse effects of most antihistamines, which include sedating effects, AR/ARC leads to school absences and poorer performance due to distraction, fatigue and irritability. AR/ARC often produce embarrassment feelings which results in a poor interaction by peers, thus leading to isolation and low self-esteem. In addition, it also has a negative impact on the parents HRQoL, who frequently become anxious, overprotective and sometimes results on absenteeism.

Illness comprehension by adolescents, particularly as they get older, influences their HRQoL and may be an important target for intervention aimed at improving their psychological well-being (13).

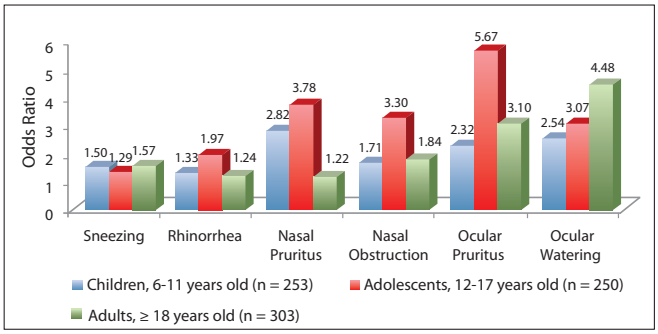
Despite the impact of AR on HRQoL of both adults and children, it is interesting how symptom perception differs in children, adolescents and older patients. A study performed on 806 French patients suffering from moderate-to-severe persistent ARC showed that the symptoms with highest impact on adolescents were nasal pruritus, nasal obstruction and ocular pruritus as evaluated by the rhinoconjunctivitis quality of life questionnaire (RQLQ) (**figure 2**) (14).

Few years ago, Juniper *et al*. already emphasized that the impairment of HRQoL in adolescents may not be the same as in adults and proposed a specifically designed questionnaire for adolescents with rhinoconjunctivitis (14). They propose that this questionnaire should include both physical and emotional functions, items that are important to adolescents with ARC. It should be short and include summary scores for each domain being amenable to statistical analysis and being responsive to clinically important changes.

A case-control analysis involving 1,834 students has shown that seasonal allergic rhinitis is associated with a detrimental effect on exam scores in teenagers (15). This study distinguished between cases (consisting on students who dropped 1 or more their grades) and controls (students whose grades were either unchanged or improved). Data reported that cases were significantly more likely to have been diagnosed with asthma, to have had AR symptoms during exams and to have taken AR medication or sedating antihistamines compared to controls (**figure 3**).

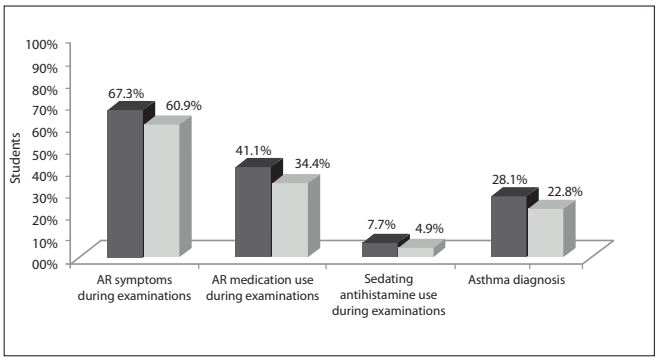
When measuring quality of life, data are collected directly from the patients, which somewhat differ from those obtained with the conventional measurement used in clinical practice. Instruments for measuring quality of life can be subdivided into generic and specific tools. The generic tools measure multi-dimensions in different health conditions whereas specific tools are focus on measuring particular aspect of a certain disease. **Table I** illustrates available questionnaires to assess HRQoL in adolescents.

***Figure 2** - Impact of symptoms on the RQLQ score.*



Odds ratio [95% CI]. Adapted from reference 13 with permission.

***Figure 3** - Association between allergic rhinitis and detrimental effect on examination in teenagers.*



Black bars: case students; grey bars: control students; OR: odds ratio; adapted from reference 15.

Treatment burden impact of AR and ARC

A study with the primary aim of validating a health-related QoL assessment in adolescents with rhinoconjunctivitis, asthma or both, has also reported on treatment aspects of these conditions, and found that a high proportion of adolescents are bothered by having to take medications and by experiencing bothersome medication adverse effects (AEs). The new QoL assessment tool proposed in this study, RHINASTHMA-Adolescents questionnaire, is comprised of 20 questions. The results of this survey revealed that the items with the greatest impact in HRQoL of adolescent patients were the following: feeling uncomfortable (81.4%), having a stuffy nose (68.2%), feeling

Table I *- Available questionnaires to assess HRQoL in adolescents.*

Author	Year	Description
Cui W *et al.* (16)	2013	Trends in adolescent HRQOL were assessed by using cross-sectional data from the 2001–2010 National Health and Nutrition Examination Survey. Adolescents' self-rated health and reported mental health declined significantly, especially among those in low-income families, but their physical health and activity limitation did not change.
Kim JH *et al.* (17)	2014	QOL-KCAR assessment tool comprising 10 questions was developed to assess the practical difficulties experienced in daily activities of Korean children with allergic rhinitis.
Juniper EF *et al.* (18)	1998	The Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) measures the quality of life impairments important to children with SAR. Children provide reliable and accurate responses, the measurement properties are strong.
Petersen DK *et al.* (19)	2008	The 15D instrument and the RQLQ instrument were capable of differentiating RC patients across different disease severities.
CDC (20)	2000	Medical Outcomes Study Short Forms (SF-12 and SF-36), the Sickness Impact Profile, and the Quality of Well-Being Scale.

limited in their social life (73.2%), being stressed by their parents (73.8%), breathing with difficulty (71.3%), having a runny nose (63.4%), being bothered by having to take drugs (81.9%) and the medication side effects (54.3%) (21).

Another study which surveyed parents of adolescents to assess the patient perceived burden of seasonal ARC revealed that the most important criteria for allergy medications were effectiveness, ease of use, consistency of relief, fewer AEs, rapid response and providing freedom to do more. In addition, the survey showed that the criteria that would make it easier for children to comply with medication were: convenient dosing schedule, fewer AEs, ease of use and better taste (22). Pediatric formulations of oral antihistamines and intranasal corticosteroids are available and significantly improve SAR symptoms in children and adolescents (23). Immunotherapy tablets (SLIT) can also improve HRQoL in adolescents with AR and conjunctivitis as observed in a recent two pooled double-blind placebo-controlled trials performed on 395 adolescents with house dust mite (HDM) allergic rhinitis. It can be observed a parallel increase in HDM-specific IgG4 in the active patient group after 4 weeks of treatment (24).

Perspectives

Things are changing, we are living a digital era, and treatment must be person-centered with the use of real-world evidence. In this context, ARIA (Allergic Rhinitis and its Impact on Asthma) has evolved from a guideline using the best evidence-based approach to develop care pathways suited to real-life using mobile technology in AR and asthma multimorbidity. These include a novel phenotypic characterization of the patients, confirmation of the impact of AR on work productivity and treatment patterns in real life (23). Also, mobile technology MASK (Mobile Airways Sentinel network) allows every adolescent to search and be up to date on allergic diseases.

There is some understanding of the challenges faced by adolescents with asthma, but not so much with other allergic conditions. More studies are necessary, paying particular attention to the effects of allergic co-morbidities (24, 25).

Conclusions

It can be concluded that adolescence is a special period in which AR is highly prevalent with some sex-dependent differences. There are also peculiarities on how AR affects HRQoL of adolescent patients specifically. Considering the recent advances in the field, digital aid is the future. The success of treatment lies in the partnership between adolescents with AR and mobile technology, allowing them to have more information both on the disease and treatment.

Conflict of interests

NAR reports personal fees from Sanofi, Mylan, AstraZeneca, Chiesi, Abbott, Mantecorp and Abbvie outside the submitted paper. MM-A is Manager Medical Affairs: Sanofi, Gentilly-France. CSR is sub-investigator in clinical trials for Sanofi, AstraZeneca and FioCruz.

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ORIGINAL ARTICLE | Eur Ann Allergy Clin Immunol | Vol 53, N.6, 252-262, 2021

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The psychological impact of food allergy and undergoing a food challenge test in adult age

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Key words

Food allergy; health-related quality of life; food challenge test; emotional distress; health anxiety.

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Doi
10.23822/EurAnnACI.1764-1489.187

Impact statement

Undergoing a food challenge test and excluding food allergy was found to significantly improve ealth-related quality of life (HRQoL) in adults.

Summary

Introduction. *Despite an increasing number of adults being affected by food allergy, there is currently limited research regarding the psychological impact of living with this condition in this age group and the effect of undergoing food challenge testing - the gold standard for diagnosis - on health-related quality of life (HRQoL).* ***Objective.*** *To assess whether ruling out a food allergy using an open food challenge could improve HRQoL and emotional well-being. To evaluate whether HRQoL gains are higher among people testing negative for food allergy and whether people higher on health anxiety would be less reassured by a negative food challenge.* ***Methods.*** *A cross-sectional study (n = 276) and a prospective study (n = 53) were performed. Adults with a positive (n = 34), or negative food challenge (n = 34), or with an allergy confirmed via other means (No challenge, n = 208), completed the Food Allergy Quality of Life Questionnaire-Adult Form, General Health Questionnaire-12, State-Trait Anxiety Inventory short form, Positive and Negative Affect Schedule, shortened version of the Health Anxiety Questionnaire in addition to clinical and demographic variables. A prospective study examined these measures before and three months after a food challenge (negative, n = 45; positive, n = 8).* ***Results.*** *Adults with a negative food challenge outcome had better HRQoL than those with a food allergy confirmed via other means (No challenge), with no differences between the two allergy positive groups (food challenge vs no challenge). No group differences in emotional distress, health anxiety or mood were found. The prospective study showed HRQoL significantly improved following a food challenge ($F_{(1,39)}$ = 16.868; p < 0.001; Intention-to-treat $F_{(1,52)}$ = 15.346; p < 0.001). High health anxiety was not associated with lower reassurance following a negative test.* ***Conclusions.*** *People who have a food allergy excluded following a food challenge have better HRQoL. There was a significant improvement in HRQoL following an open food challenge which supports the need to increase provision of food challenge testing in this age group.*

Introduction

Food allergies are an abnormal response of the body to otherwise harmless food proteins involving the immune system (1). The prevalence of food allergy has increased in recent decades and is now recognised as a substantial public health burden in developed countries with up to 10% affected (2, 3). Symptoms vary and can involve the skin, oropharyngeal tract, gastrointestinal tract, respiratory and cardiovascular systems, with the most severe and sometimes fatal manifestation being anaphylactic shock. Food allergy has an unpredictable nature and individuals with only mild reactions may have a severe and life-threatening reaction on re-exposure.

Although research into possible treatments for food allergy including immunotherapy is being carried out, there is currently no cure. Food allergic individuals must carefully avoid the caus-

al foods on a daily basis and carry emergency treatment such as adrenaline in case they have a reaction. Thus, living with food allergies constitutes a unique stressor that is both chronic and acute, *i.e.,* facing a daily threat of accidental allergen ingestion compounded by acute stress during allergic reactions (4).

Diagnosis of food allergy involves taking a detailed clinical history to guide the requirement for skin prick and/or serum specific immunoglobulin E (sIgE) testing. When the clinical history and tests alone cannot provide a definitive diagnosis, or when the possibility of having outgrown an allergy exists, an oral food challenge is essential (5). A food challenge involves the graded administration of the potential culprit food in order to identify if an individual is allergic or tolerant, thereby confirming or excluding a diagnosis of food allergy.

There is evidence that food allergy can lead to increased anxiety about food safety, social isolation and exclusion, and emotional pressure related to constant vigilance; impacting well-being, mental health and quality of life (6-8). While some quantitative studies have examined the effect of food challenge tests on HRQoL (9-14), the majority have been on children/adolescents or their carers. To our knowledge, only one study has included adults and was done in the context of a double-blind, placebo-controlled food challenge (DBPCFC) (14). It found that HRQoL scores improved significantly after a DBPCFC when all outcomes of the test were combined compared to a control group with greater improvements after a negative outcome when a food allergy was ruled out than a positive outcome (food allergy confirmed). However, there is a need to assess whether this is the case for open food challenges which are the type of food challenges more commonly performed in clinical practice rather than DBPCFC.

Another aspect that has received little attention in the context of food allergies is the role of health anxiety. People who are anxious about their health are more likely to misinterpret health information as personally threatening (15, 16); show adverse emotional reactions to ambiguous diagnostic test results, and are less reassured following the medical investigation of symptoms, even when there is no evidence of disease (*e.g.,* 17, 18). Based on these findings, people with high health anxiety may be less reassured by a negative allergy test than people low on health anxiety.

The present study was designed to assess the psychological impact of food allergy and open food challenges on HRQoL, emotional distress, health anxiety and negative mood in an adult population.

Based on previous research we predicted that: 1) there would be better HRQoL and lower emotional distress, health anxiety and negative mood in people who test negative following a food challenge test; 2) HRQoL would improve among all people undergoing a food challenge test, but to a greater extent among people testing negative; 3) People higher on health anxiety would be less likely to be reassured by a negative food challenge.

Materials and methods

Design

This research consisted of two studies:

1. a cross-sectional study that compared HRQoL and psychological measures among adults with clinician confirmed food allergy diagnosis (based on clinical history, skin prick and/or serum sIgE testing) *vs* adults who had undergone a food challenge test;
2. a prospective study that examined changes among people undergoing a food challenge test.

A negative challenge was defined as tolerating the food without any evidence of allergic symptoms, thus allergy to the food tested was excluded while a positive outcome required the presence of symptoms and objective signs consistent with IgE mediated food allergy.

Ethical considerations

The North East-Sunderland National Research Ethics Service (NRES) Committee approved this research project in September 2013 (REC reference: 13/NE/0271). Following this, Research and Development approval was sought from the Royal Brompton and Harefield NHS Foundation Trust and was granted (2013AT007B). The research was conducted in accordance with the ethical standards established in the Declaration of Helsinki and informed consent was obtained from all participants before enrolment in the studies.

Recruitment and participants

Study 1

Individuals that had previously attended the Allergy Department at Royal Brompton & Harefield NHS Foundation Trust, London and were diagnosed with food allergy based on clinical history, skin prick and/or sIgE tests (Group 1-FA-No challenge) or who had previously undergone a clinically indicated food challenge (Group 2-Food Challenge) were identified from the medical records. The inclusion criteria for participating in this study were aged 18 or older, clinician confirmed IgE mediated food allergy or previous food challenge. Individuals could not participate if they were considered adults with incapacity.

Study 2

All individuals who were waiting to have a food challenge test between October 2013 to March 2015 were invited to participate in the study. Fifty-six individuals were eligible to participate.

Measures

Demographic characteristics

Participants were asked to record their age, gender, ethnicity and educational qualifications.

Food allergy characteristics
Specifically designed questions were used to assess the foods that previously caused allergic symptoms, age when first experienced a reaction, treatment received, investigations for food allergy and adrenaline auto-injector possession. Participants who had undergone a food challenge test were asked about the number and type of food/s they had tested, time between the initial reaction and the food challenge test to the suspect food and outcome of the challenge.

Health-related quality of life
The FAQLQ-Adult Form was used in this study as this is the only disease-specific HRQoL questionnaire for food allergic adults (19), using a 5-point Likert scale with response options: 0: not at all, 1: slightly, 2: moderately, 3: very and 4: extremely. It has four subscales which can be combined to generate a total HRQoL score:

1. Allergen Avoidance and Dietary Restrictions (AADR), example item "*How troublesome do you find it that you have to be alert to what you are eating?*";
2. Emotional Impact (EI), example item "*How frightened are you of accidentally eating the wrong food?*";
3. Risk of Accidental Exposure (RAE), example item "*How troublesome is it that labels are incomplete?*";
4. Food Allery related Health (FAH), example item "*How worried are you that it is unclear to which foods you are allergic?*".

In Study 1, participants who had undergone a food allergy challenge test were asked to complete this in relation to their perceived quality of life now and prior to completing the challenge test. In Study 2 participants completed the questionnaire before the food challenge and three months after.

Emotional distress
Emotional distress was measured using the 12-item version of the General Health Questionnaire (GHQ-12) (20). Responses were scored 0-3 and were summed to produce a scale from 0 to 36, with higher scores indicating greater distress.

State anxiety
State anxiety was assessed with the validated 6-item version of the Spielberger State Trait Anxiety Inventory (STAI) with response options on a 6 point scale (21). Responses were totalled giving a score of between 6 and 24, with higher scores indicating higher anxiety.
Positive and Negative Affect was measured using the Positive and Negative Affect Schedule (PANAS) (22). Participants were asked how they feel "right now". Participants were asked to rate the extent to which they experienced each of the emotions on a 5-point Likert scale ranging from "very slightly or not at all" to "extremely". Both subscales range from 10 (low) to 50 (high).

Health anxiety
A shortened version of the Health Anxiety Questionnaire (HAQ) (23, 17) was used in this study in order to assess the presence of health anxiety in our study population. Participants responded using a 4-point Likert scale "not at all or rarely", "sometimes", "often", "most of the time", with responses averaged to give scores from 1 to 4, with higher scores indicating higher levels of health anxiety.

Co-morbidities
Participants were asked whether they suffered from any other allergic conditions or any other medical conditions.
Reassurance following a negative test was assessed with the following items: "If your test to any food was NEGATIVE (*i.e.* no symptoms) how reassured are you that you are not allergic to that food?". Response options were: "Not at all", "Slightly", "Moderately", "Very" and "Extremely".

Food re-introduction
Participants were also asked if they had re-introduced the food back into their diet if their food challenge test was negative (response options: "Yes, small amounts", "Yes, normal amounts", "No, still avoiding" or "No, haven't re-introduced but not avoiding"). If they had not re-introduced it, what were the reasons (response options: "Fear of reaction", "Not convinced of negative test", "Reaction on eating food after challenge", "Not confident to try alone", "Other"). If your challenge was negative, does this mean that you no longer need to carry any emergency medication? "Yes" "No, I have other allergies".

Procedure
All potential participants were provided with an information sheet including details about the study and a copy of the questionnaire. They were informed that participation was voluntary and that they had the right to withdraw at any time during the study. Furthermore, declining to take part in the study would have no impact on their care. They were also provided with the researchers contact details in case they had any questions about the research. If they wished to take part, they had to give written informed consent and complete the questionnaire provided with the information sheet and return in the enclosed stamped self-addressed envelope.

Data analyses
Statistical analyses were performed using SPSS software (IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp). Differences between groups were assessed using either General linear model (GLM) for continuous data or chi-square/Fisher's exact test for categorical data. Linear regression was used to assess differences between the groups on measures of HRQoL, emotional distress, health anxiety and mood. GLM was used

to assess change in HRQoL between the two food challenge groups. The percentage of missing data was less than 5%.

The sample size was calculated to detect a medium effect size (Cohen's f^2 = 0.15/ Cohen's f = 0.25) at 80% power and 5% significance level. For the linear regression, assuming ten predictors, the sample size was 118. For GLM to detect changes in pre- and post-challenge HRQoL scores for 2 groups (food challenge positive or negative) across two time points (before and three months after the test), the total sample size was 34 (G*Power, version 3.1.7) (24).

Results

Study 1

In total 276 individuals participated. Group 1 (FA-No challenge) consisted of adults with clinician confirmed food allergy but who had not undergone a food challenge test. The response rate for Group 1 was 83.2% with 208 adults (69.7% female, n = 145) consenting to participate out of 250 eligible individuals. Group 2 (Food Challenge) included 68 adults who had previously undergone a food challenge test. All challenge tests were clinically indicated either for diagnostic purposes *i.e.,* inconclusive skin prick/sIgE tests or to assess if individuals had outgrown an allergy *i.e.,* suspected to no longer be allergic. The response rate for this group was 59.1% (68 out of eligible 115 individuals participated). Fifty percent of the 68 participants (n = 34) had a negative challenge outcome *i.e.,* allergy to tested food excluded (FC-Negative) and 50% (n = 34) had a positive challenge test to a food (FC-Positive) *i.e.* allergy confirmed.

In the total study sample (n = 267), the majority were female (69.2% n = 191), had educational qualifications (97.8%, n = 261), and identified their ethnicity as White (73.6%, n = 203). There were significant differences between the groups in age ($F_{(2,273)}$ = 4.138; p = 0.017); post-hoc comparisons showed the FC-Positive group were significantly older than Group 1 (p = 0.024), but there was no difference in age between the FC-Positive and FC-Negative subgroups (p = 1.000). There were no significant differences between the groups in terms of gender, ethnic group, or educational level (**table I**).

As is common in individuals with food allergies, many of the participants suffered with other allergic conditions. These included: asthma 59.1% (n = 163) and allergic rhinitis 68.8% (n = 190), although prevalence of other comorbidities such as heart disease was low. The FC-Positive group were more likely to have asthma than Group 1 (OR: 3.559, 95% CIs: 1.414 to 8.962, p < 0.007), and the FC-Negative group (OR: 4.667, 95% CIs 1.540 to 14.143, p = 0.006) with no difference between the FC-Negative group and Group 1 (OR: 1.311, 95% CIs: 0.634 to 2.710, p = 0.465). There were no differences between the groups on other allergies or comorbidities.

Food allergy profile, diagnosis and treatment

Food allergy profiles across the groups are shown in detail in **table II**. Forty-nine percent (n = 112) reported that they had previously experienced symptoms consistent with anaphylaxis. There were no significant differences between the groups in terms of age of allergy onset, food type, anaphylaxis and treatment received. There was a significant difference in gastrointestinal (GI) symptoms between groups, with the FC-Negative less likely to report GI symptoms than Group 1 (p = 0.017), but no differences between the other comparisons (FC-Negative *vs* FC-Positive; FC-Positive *vs* Group 1). There were no significant differences between the groups on the other symptoms.

Among participants who underwent a food challenge, the mean length of time between first experiencing symptoms to the suspect food and undergoing a food challenge to that food was 12.47 years, ranging from one month to 50 years.

Adrenaline auto-injector possession

65.2% (n = 180) of all participants reported that they were advised to and were carrying adrenaline auto-injector devices. There was a significant reduction in the proportion of people who reported carrying an adrenaline autoinjector who tested negative in the food challenge, (85.3%, n = 29 pre-challenge *vs* 61.8%, n = 21 post-challenge; p = 0.021). In the FC-Positive group there was no significant change (52.9 %, n = 18 pre-challenge *vs* 67.6%, n = 23 post-challenge; p = 0.227).

Health-related quality of life

The FC-Negative group reported better HRQoL than Group 1, even after adjusting for age, presence of asthma and GI symptoms (factors that had differed across the three allergy groups). There was no difference in total HRQoL scores between the two groups with confirmed food allergy (FC-Positive *vs* Group 1) in both unadjusted and adjusted analyses (**table III**). Presence of both asthma and GI symptoms were predictive of poorer HRQoL (p = 0.006 and p < 0.001 respectively). The same pattern of significant results was seen in the HRQoL sub-scales AADR and FAH. No differences were observed between the FC-Positive or FC-Negative groups in comparison with Group 1 once the Bonferroni correction had been applied.

Emotional distress and mood

There were no differences between the three groups on emotional distress, state anxiety, or positive and negative affect. The FC-Positive group reported lower levels of health anxiety than Group 1 in both unadjusted and adjusted analyses, although this was no longer significant following a Bonferroni correction (**table III**).

Change in HRQoL in food challenge group

The GLM analysis showed a significant effect of time, with improvements in HRQoL ($F_{(1,66)}$ = 44.40, p < 0.001). There was a non-significant trend between outcome of challenge and change

Table I *- Socio-demographic characteristics and co-morbidities of participants in Study 1.*

	Overall (N = 276)	**Group 1 Food Allergy No challenge (n = 208)**	**Group 2 Challenge Positive (n = 34)**	**Group 2 Challenge Negative (n = 34)**	**Group differences**
Age (years), mean (sd)	38.09 (15.02)	36.71 (14.36)	44.03[a] (16.96)	40.68 (15.51)	P = 0.017
Gender % female (n)	69.2 (191)	69.7 (145)	67.6 (23)	67.6 (23)	P = 0.950
Ethnic group %, (n)					
White	73.6 (203)	71.6 (149)	82.4 (28)	76.5 (26)	P = 0.388 (white *vs* non-white)
Mixed/multiple ethnic	5.8 (16)	7.2 (15)	0 (0)	2.9 (1)	
Asian/Asian British	12.3 (34)	13.5 (28)	8.8 (3)	8.8 (3)	
Black/African/ Caribbean/Black British	5.1 (14)	4.8 (10)	5.9 (2)	5.9 (2)	
Other	3.2 (9)	2.9 (6)	2.9 (1)	5.9 (2)	
Highest Qualification					P = 0.862 +
Degree or equivalent	70.0 (187)	69.5 (139)	66.7 (22)	76.5 (26)	
Below degree level	27.7 (74)	28.0 (56)	30.3 (10)	23.5 (8)	
No qualifications	2.2 (6)	2.5 (5)	3.0 (1)	0 (0)	
Co-morbidities					
Allergic					
Asthma	59.1 (163)	56.7 (118)	82.4 (28)[a]	50 (17)[b]	P = 0.010
Rhinitis	68.8 (190)	69.7 (145)	61.8 (21)	70.6 (24)	P = 0.633
Atopic dermatitis	48.9 (135)	49.5 (103)	50 (17)	44.1 (15)	P = 0.835
Eosinophilic oesophagitis	0.7 (2)	0.5 (1)	2.9 (1)	0 (0)	P = 0.433 +
Other					
Heart disease	1.4 (4)	0.7 (3)	0 (0)	2.9 (1)	P = 0.680 +
Diabetes	2.9 (8)	2.4 (5)	5.9 (2)	2.9 (1)	P = 0.467 +
Epilepsy	1.8 (5)	1.9 (4)	0 (0)	2.9 (1)	P = 0.760 +
Stroke	0.4 (1)	0.5 (1)	0 (0)	0 (0)	P = 1.000 +
Arthritis	9.1 (25)	8.2 (17)	17.6 (6)	4.9 (2)	P = 0.212 +
Mental/Emotional disorder	8.7 (24)	8.7(18)	5.9 (2)	11.8 (4)	P = 0.673 +
Other illness	18.5 (52)	20.7 (43)	8.8 (3)	17.6 (6)	P = 0.275 +

Valid percent where people indicated they did not wish to answer; +: Fisher's exact; [a]Significant difference between FC-Positive group and Group 1 (FA-No challenge group); [b]Significant difference between FC-Positive and FC-Negative groups.

in HRQoL, $F_{(1,66)} = 3.077$, p = 0.084, with a higher improvement in HRQoL scores in the challenge negative than the challenge positive group (0.762 *vs* 0.445 respectively).

There were differences between the FC-Negative *vs* FC-Positive in presence of asthma. When this was entered into the model, improvement in HRQoL over time remained significant (p < 0.001) and the interaction became non-significant (p = 0.214).

Reassurance in results

The mean levels of reassurance following a negative outcome were 3.882 (SD = 1.274), with 47.1% (n = 16) responding "extremely", 17.6% (n = 6) "very", 14.7% (n = 5) "moderately", 17.6% (n = 6) slightly and 2.9% "not at all" reassured. The correlation between health anxiety and reassurance for people testing negative was - 0.076, p = 0.670.

Food re-introduction

Participants with a negative challenge outcome responded that 76.5% had re-introduced the food tested back into their diet in normal amounts or small amounts. 2.9% had not re-introduced but were not specifically avoiding while 20.6% were still avoiding. The reasons given by those still avoiding were: fear of reaction (n = 2), not confident to try alone (n = 4) and reaction on eating food after challenge (n = 1).

Study 2

Fifty-three out of 56 eligible individuals,45 tested negative, and only 8 tested positive.

The mean age of the 53 participants was 33.5 years (SD = 12.5) with a range of 18 to 62 years. 71.7% were female, 84.9% (n =

Table II *- Allergy profile characteristics of participants per group in Study 1.*

Allergy profile	**Group 1 Food Allergy-No challenge (n = 208)**	**Group 2 Challenge Positive (n = 34)**	**Group 2 Challenge Negative (n = 34)**	**Group differences**
Age first experienced food allergy, mean (sd)	20.35 (17.9)	25.82 (20.75)	24.15 (21.62)	p = 0.198
Food involved % (n)				
Peanut	39.9 (83)	38.2 (13)	38.2 (13)	p = 0.971
Tree nuts	41.8 (87)	41.2 (14)	35.3 (12)	p = 0.772
Fish	15.9 (33)	14.7 (5)	20.6 (7)	p = 0.759
Shellfish	25.5 (53)	32.4 (11)	32.4 (11)	p = 0.543
Milk	13.5 (28)	14.7 (5)	14.7 (5)	p = 0.874 +
Egg	16.3 (34)	14.7 (5)	17.6 (6)	p = 0.947
Wheat	12.5 (26)	5.9 (2)	5.9 (2)	p = 0.434 +
Soy	13.9 (29)	14.7 (5)	5.9 (2)	p = 0.491 +
Sesame	8.7 (18)	14.7 (5)	11.8 (4)	p = 0.454 +
Celery	8.2 (17)	14.7 (5)	0 (0)	p = 0.051 +
Mustard	3.4 (7)	8.8 (3)	2.9 (1)	p = 0.313 +
Lupin	3.8 (8)	2.9 (1)	5.9 (2)	p = 0.866 +
Fruits/vegetables	51.4 (107)	50.0 (17)	35.3 (12)	p = 0.217
Other	38.9 (81)	32.4 (11)	50.0 (17)	p = 0.313
Number of foods involved in reactions, mean (sd)	3.34 (2.35)	3.35 (2.70)	2.91 (1.87)	p = 0.610
Symptoms				
Oropharyngeal	77.9 (162)	61.8 (21)	67.6 (23)	p = 0.082
Skin (rash/urticaria/eczema)	61.5 (128)	67.6 (23)	67.6 (23)	p = 0.663
Angioedema	76.9 (160)	76.5 (26)	73.5 (25)	p = 0.911
Upper respiratory	36.5 (76)	23.5 (8)	32.4 (11)	p = 0.322
Lower Respiratory	56.3 (117)	73.5 (25)	67.6 (23)	p = 0.099
Gastrointestinal	46.2 (96)	41.2 (14)	23.5 (8)[c]	p = 0.046
Other	6.7 (14)	8.8 (3)	11.8 (4)	p = 0.467 +
Anaphylaxis	38.9 (81)	41.2 (14)	50.0 (17)	p = 0.475
Treatment received				
Antihistamines	84.6 (176)	94.1 (32)	94.1 (32)	p = 0.180 +
Steroids	42.8 (89)	47.1 (16)	52.9 (18)	p = 0.518
Adrenaline	32.7 (68)	50.0 (17)	47.1 (16)	p = 0.061
No treatment	8.2 (17)	2.9 (1)	2.9 (1)	p = 0.508 +

+: Fisher's exact; [c]Significant difference between Group 1 (FA-No Challenge) and FC-Negative groups.

45) had educational qualifications and the majority identified their ethnicity as White (69.8%, n = 37). Many of the participants suffered with other allergic conditions in particular, asthma 62.3% (n = 33), allergic rhinitis 60.4% (n = 32) and atopic dermatitis 49.1% (n = 26).

The sample included participants with a range of food allergies and symptoms. The mean number of foods that participants reported as having previously experienced symptoms to was 3.09 (SD = 2.41, range 1 to 11 foods). 47.2% had experienced symptoms to peanut, 43.4% to tree nuts, fruits 37.7%, shellfish 34%, fish 24.5% as well as a variety of other foods. The symptoms experienced included oropharyngeal 64.2%, skin 71.7%, upper airway 30.2%, respiratory (lower airway) 43.4%, gastrointestinal 50.9% and anaphylaxis 37.7%. The mean age when individuals first experienced allergic symptoms to any food was 20.5 years (SD = 16.4, rang 6 months to 56 years).

The most common foods that were tested with food challenge were tree nuts (34%, n = 18), shellfish (24.5%, n = 13), peanut (20.8%, n = 11), and fish (17%, n = 9). The average time between first experiencing symptoms to a food and undergoing a challenge test to the suspect food was 8.58 years (SD = 9.18) (range 3 months to 32 years; median 3 years).

Table III *- Quality of life, emotional distress, health anxiety and mood among participants with different allergy tests and test outcomes Study 1. Numbers are means (SDs).*

		Comparison with food challenge positive					Comparison with food challenge negative				
Variables	Confirmed allergy (no food challenge)	Food challenge positive	Unadjusted difference (95% CIs)	p value	Adjusted difference[d] (95% CIs)	p value	Food challenge negative	Difference (95% CIs)	p value	Adjusted difference[d] (95% CIs)	p value
Quality of life total score	1.950 (0.931)	1.916 (0.906)	- 0.034 (- 0.374 to 0.306)	0.844	- 0.121 (- 0.449 to 0.206)	0.206	1.362 (0.969)	- 0.588 (- 0.927 to - 0.248)	< 0.001*	- 0.458 (- 0.779 to - 0.136)	0.005*
Allergen Avoidance & Dietary Restrictions	2.021 (1.030)	2.099 (1.093)	0.078 (- 0.305 to 0.461)	0.689	- 0.029 (- 0.393 to 0.334)	0.874	1.340 (1.147)	- 0.681 (- 1 .065 to - 0.298)	< 0.001*	- 0.518 (- 0.875 to - 0.161)	0.005*
Emotional Impact	2.070 (1.052)	2.185 (0.968)	0.115 (- 0.267 to 0.497)	0.554	0.038 (- 0.332 to 0.408)	0.840	1.571 (1.108)	- 0.499 (- 0.880 to - 0.117)	0.011	- 0.348 (- 0.711 to 0.016)	0.061
Risk of Accidental Exposure	1.814 (1.098)	1.890 (1.066)	0.075 (- 0.327 to 0.478)	0.712	- 0.077 (- 0.458 to 0.305)	0.692	1.489 (1.182)	- 0.325 (- 0.727 to 0.077)	0.112	- 0.178 (- 0.552 to 0.197)	0.351
Food Allergy related Health	1.894 (1.054)	1.490 (1.039)	- 0.404 (- 0.775 to - 0.033	0.033	- 0.417 (- 0.799 to - 0.036)	0.032	1.049 (0.744)	- 0.845 (- 1 .217 to - 0.474)	< 0.001*	- 0.787 (- 1 .162 to - 0.412)	< 0.001*
Emotional distress (GHQ-12)	12.250 (6.851)	12.618 (7.194)	0.368 (- 2.105 to 2.840)	0.770	- 0.042 (- 2.499 to 2.583)	0.974	10.000 (5.939)	- 2.250 (- 4.723 to 0.223)	0.074	- 1 .896 (- 4.391 to 0.598)	0.136
Health anxiety	0.768 (0.645)	0.529 (0.412)	- 0.239 (- 0.457 to - 0.020)	0.032	- 0.281 (- 0.506 to - 0.055)	0.015	0.588 (0.439)	- 0.180 (- 0.398 to 0.038)	0.106	- 0.176 (- 0.397 to 0.045)	0.119
State anxiety	11.237 (3.820)	11.588 (4.076)	0.352 (- 1 .026 to 1.729)	0.616	0.418 (- 1 .009 to 1.845)	0.564	10.000 (3.191)	- 1 .237 (- 2.614 to 0.141)	0.078	- 1 .079 (- 2.479 to 0.321)	0.130
PANAS positive	27.962 (9.354)	28.745 (9.174)	0.784 (- 2.599 to 4.167)	0.649	0.759 (- 2.754 to 4.272)	0.671	28.853 (8.992)	0.891 (- 2.492 to 4.272)	0.604	0.897 (- 2.552 to 4.345)	0.609
PANAS negative	15.207 (6.059)	15.265 (6.166)	0.058 (- 2.127 to 2.243)	0.958	0.042 (- 2.223 to 2.308)	0.971	13.559 (5.445)	- 1 .648 (- 3.833 to 0.538)	0.139	- 1 .492 (- 3.716 to 0.732)	0.188

[a]No missing data; [b]missing data < 5%; [c]missing data > 5%; [d]adjusted for age, asthma and gastrointestinal symptoms; *Significant at p < 0.006 (p adjusted for multiple comparisons).

Health-related quality of life

Change in HRQoL over time was computed for responders to the follow-up questionnaire, and using an intention-to-treat analysis, where baseline scores of non-responders were used as follow-up scores, thereby assuming no change in HRQoL (**table IV**).

In the 40 participants who completed the questionnaires at all time points, there was a significant change from before and after the challenge test in mean total score $F_{(1,39)} = 16.868$, $p < 0.001$. Intention to treat analysis was also significant ($F_{(1,52)} = 15.346$; $p < 0.001$).

Significant differences were observed across all four subscales of the HRQoL questionnaire, although applying a Bonferroni correction (adopting a revised p value of p = 0.01) meant the change in RAE was no longer significant (**table V**).

Emotional distress and mood

There were no significant changes in emotional distress, health anxiety, state anxiety or positive mood over time (**table VI**). There were significant differences over time in both the PANAS-negative score and state anxiety, due to lower anxiety and negative

Table IV *- HRQoL at baseline and three months post-challenge in Study 2. Means (standard deviation).*

	Baseline HRQoL Mean	Post-challenge HRQoL Mean	Change in HRQoL Mean	Significance
Challenge outcome (N = 40)				
All participants	1.942 (0.887)	1.420 (1.038)		$F_{(1,39)} = 16.868$; $p < 0.001$
Negative (n = 33)	2.027 (0.855)	1.456 (1.117)	0.572 (0.842)	$F_{(1,32)} = 15.231$; $p < 0.001$
Positive (n = 7)	1.538 (0.992)	1.254 (0.555)	0.284 (0.577)	$F_{(1,6)} = 1.695$; $p = 0.241$
Intention-to-treat (N = 53)				
All participants	2.010 (0.860)	1.616 (0.142)		$F_{(1,52)} = 15.346$; $p < 0.001$
Negative (n = 45)	2.078 (0.835)	1.659 (1.088)	0.419 (0.762)	$F_{(1,44)} = 13.628$; $p = 0.001$
Positive (n = 8)	1.624 (0.950)	1.375 (0.618)	0.249 (0.544)	$F_{(1,7)} = 1.671$; $p = 0.237$

Table V *- Quality of life subscales means (and standard deviation). Study 2.*

	Baseline	3 months post-challenge	Significance
Completers of both time points (N = 40)			
Allergen Avoidance and Dietary Restrictions	2.023 (0.988)	1.441 (1.143)	$F_{(1,39)} = 11.790$; $p < 0.001$
Emotional Impact	2.049 (0.950)	1.579 (1.121)	$F_{(1,39)} = 10.485$; $p = 0.002$
Risk of Accidental Exposure	1.728 (1.069)	1.378 (1.214)	$F_{(1,39)} = 5.741$; $p = 0.021$
Food allergy related Health	1.967 (1.124)	1.283 (1.080)	$F_{(1,39)} = 24.471$; $p < 0.001$
Intention to treat analysis (N = 53)			
Allergen Avoidance and Dietary Restrictions	2.003 (0.946)	1.564 (1.091)	$F_{(1,52)} = 11.045$; $p = 0.002$
Emotional Impact	2.150 (0.940)	1.795 (1.124)	$F_{(1,52)} = 9.898$; $p = 0.003$
Risk of Accidental Exposure	1.835 (1.032)	1.571 (1.181)	$F_{(1,52)} = 5.576$; $p = 0.022$
Food allergy related Health	2.050 (1.108)	1.535 (1.153)	$F_{(1,52)} = 21.341$; $p < 0.001$

mood after the test than at baseline, but no differences between baseline and three months post-challenge (**table VI**).

Adrenaline auto-injector possession

Prior to the challenge, 60.4% (n = 32) of participants in the whole sample (n = 53) reported that they possessed adrenaline auto-injector devices. Following the challenge only 50.9% (n = 27) still required these.

In the group who tested negative (n = 45), the change in proportion of people carrying adrenaline autoinjectors approached significance (60%, n = 27 *vs* 49%, n = 22, p = 0.063). There was no difference in the challenge positive group, but the sample size was very small.

Reassurance in results

The mean levels of reassurance following a negative outcome were 4.000 (SD = 1.247), with 46.4% (n = 13) responding "extremely", 25.0 % (n = 7) "very", 17.9% (n = 5) "moderately", 7.1% (n = 2) slightly and 3.6 % (n = 1) "not at all" reassured. The correlation between health anxiety and reassurance for people testing negative was - 0.047, p = 0.812.

Food re-introduction

Three months after the challenge, 95% of participants had introduced the food tested into their diet (50% normal amounts, 45% small amounts). The reasons given by the 5% still avoiding the food were: fear of reaction, not confident to try alone, reaction on eating food after challenge and not convinced of the negative test.

Discussion

We examined HRQoL, emotional distress, health anxiety and mood among adults undergoing a food challenge, using both

Table VI *- Psychological measures over time. Study 2. Means (SD).*

	Baseline	Immediately after the challenge	3 months post-challenge	Significance
Completers only (N = 40)				
Health anxiety	0.613 (0.503)	-	0.725 (0.476)	$F_{(1,39)} = 2.983$; $p = 0.092$
GHQ-12	11.400 (5.339)	-	10.650 (6.904)	$F_{(1,39)} < 1$; $p = 0.446$
STAI state anxiety	11.100 (3.926)	8.050 (2.087)	10.200 (3.244)	$F_{(1.780,69.421)} = 15.038$, $p < 0.001$
PANAS positive	28.125 (8.519)	29.025 (10.726)	29.150 (8.463)	$F_{(2,78)} < 1$; $p = 0.705$
PANAS negative	14.300 (4.262)	11.050 (1.724)	13.100 (4.454)	$F_{(2,78)} = 9.642$; $p < 0.001$
Intention to treat analysis (N = 53)				
Health anxiety	0.609 (0.547)	-	0.693 (0.532)	$F_{(1,52)} = 2.946$; $p = 0.092$
GHQ-12	11.491 (6.021)	-	10.925 (7.130)	$F_{(1,52)} < 1$; $p = 0.445$
STAI (state anxiety)	10.811 (3.878)	8.283 (2.545)	10.132 (3.334)	$F_{(2,104)} = 15.75$; $p < 0.001$
PANAS positive	28.057 (8.534)	27.755 (10.258)	28.830 (8.510)	$F_{(2,104)} < 1$; $p = 0.609$
PANAS negative	14.774 (5.542)	11.642 (3.437)	13.868 (5.755)	$F_{(2,104)} = 14.773$; $p < 0.001$

cross-sectional and prospective study designs. Study 1 showed that adults who had tested negative (FC-Negative) reported better HRQoL than people living with a clinician diagnosed food allergy who had not undergone a food challenge (Group 1). There were no differences in HRQoL between the FC-Positive group and Group 1. These results remained significant controlling for age, and presence of asthma or GI symptoms, which varied between the groups. The groups did not differ in relation to emotional distress, health anxiety or positive and negative mood. However, the overall sample mean for GHQ-12 was above the scores of 11-12 which is considered to indicate a risk of being diagnosed with a mental illness (20) thus showing that some food allergic adults have high levels of psychological distress.

Consistent with previous research (14) there were significant improvements in HRQoL over time. The retrospective study (Study 1) showed significant changes in total HRQoL scores, with improvements in two out of four of the subscales (Allergen Avoidance & Dietary Restrictions and Food allergy related Health), while the prospective study (Study 2) showed significant improvements in three, with positive changes also observed in Emotional Impact. This suggests people may have greater difficulty recalling the emotional impact of an allergy than other aspects. Following a negative challenge, fewer individuals reported a need to carry adrenaline auto-injector devices than those with a positive test. However, it is not clear why the FC-Negative group did not report lower levels of Risk of Accidental Exposure when they have had allergies to particular food groups ruled out.

Contrary to predictions we found no differences in HRQoL among people testing positive compared with those testing negative. In Study 1, the interaction between time and food challenge outcome approached significance, but once group differences in the prevalence of asthma were controlled for, the interaction became non-significant. Having asthma was a significant independent predictor of HRQoL which is consistent with previous findings (8). Food allergies often co-exist with asthma (25), and can also trigger or worsen asthma symptoms making this relationship more complex (26). Study 2 had too few positive challenge outcomes to test for group differences in HRQoL. Previous research has shown people testing positive also report increases in quality of life, although to a lesser extent than people testing negative (14). The benefits of a positive test include greater certainty about which foods to avoid, allowing the affected individual to develop adaptive strategies to better manage their condition that may lead to improvements in HRQoL.

A novel aspect of this study was that health anxiety was also measured that has not been studied previously in food allergic individuals. Health anxiety refers to apprehension and fear that changes in bodily sensations may be indicative of a serious illness (16). Individuals with high health anxiety often fail to be reassured by medical tests (*e.g.,* 17). However, among the negative challenge participants, there was no significant association between reassurance and health anxiety, but this part of the study was underpowered. Following a negative challenge, individuals are advised that they can introduce the food that they were avoiding back into their diets. In Study 2, 95% of

participants re-introduced the food. However, in Study 1 only 76.5% had done so. This is an area that requires further studying in order to understand the reasons why individuals may not be convinced or trust the result to eat the food again.

Of concern is the average time participants reported between first experiencing symptoms to a food and undergoing a challenge test to the suspect food: 12.47 years in Study 1 and 8.58 years Study 2. This may also reflect the lack of education of the public regarding food allergies in adults as well as the limited adult allergy services in the UK and the provision of food challenge tests. There is now also evidence that delaying food challenge tests is associated with direct and indirect economic costs (27, 28).

Strengths and limitations

A strength of this study is that it explored an area and a population that has received little attention, exploring HRQoL in adults with clinician-diagnosed food allergy and who had undergone a clinically indicated open food challenge in the UK using a disease specific questionnaire. Furthermore, emotional psychological distress, mood and health anxiety were assessed which has also not been explored in this group.

The large sample of food allergic adults allowed for inclusion of participants with different ages and types of food allergies. However, a larger prospective study is needed to adequately assess whether FC-Positive and FC-Negative groups differ in relation to HRQoL, and to assess the relationship between health anxiety and failure to be reassured following a negative test.

In the prospective study, participants were followed at three months after the challenge test. Future studies can potentially assess HRQoL at longer periods of time after challenge to assess whether this benefit from undergoing a challenge test is maintained as was the case in the retrospective study. Strategies for achieving a good response rate will need to be considered as in this study we found the response rate for the follow up questionnaire was reduced.

In addition, a multi-centre as opposed to a single centre study, may have strengthened the external validity of our findings and reduced any potential bias due to other aspects of care received by participants that may have positively impacted on their experience.

Conclusions

The findings from this research indicate that the issues of living with food allergy faced by adults have a negative impact on their HRQoL. Undergoing an open food challenge test was found to significantly improve HRQoL. By making these tests more widely available in clinical practice and clarifying whether an individual is allergic or not, any uncertainty can be dispelled, unnecessary food restrictions can be avoided and HRQoL can be improved.

Conflict of interests

The authors declare that they have no conflict of interests.

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Omalizumab in severe chronic urticaria: are slow and non-responders different?

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Key words
Chronic Urticaria; omalizumab; biomarkers; IgE; thyroid autoimmunity.

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Doi
10.23822/EurAnnACI.1764-1489.167

Summary
Background. *The response to omalizumab by patients with severe chronic spontaneous urticaria (CSU), may be rapid, slow, or absent. An early response has been associated with an IgE-mediated auto-allergic pathogenic mechanism, whereas little is known about slow and non-responders.* ***Objective.*** *To compare CSU patients responding slowly or non-responding to omalizumab.* ***Methods.*** *Forty-six patients showing a slow (n = 23) or absent (n = 23) response to omalizumab out of a cohort of 170 patients with severe CSU (UAS-7 > 30) were studied. Several baseline clinical and serological parameters were compared in the two groups.* ***Results.*** *Apart from a lower prevalence of atopic diseases ($p < 0.05$) and a slightly higher prevalence of thyroid autoimmunity in non-responders, the two groups were similar in terms of clinical and serological features. The majority of patients in both groups showed low baseline total IgE levels.* ***Conclusions.*** *Patients with severe CSU showing a slow response or not responding at all to omalizumab show impressive similarities. It is currently not possible to predict whether patients with severe CSU and low IgE levels will show a slow response or will not respond to anti-IgE treatment.*

Impact statement
CSU patients responding slowly or not responding to omalizumab are very similar, the latter showing only a lower prevalence of atopic diseases and a slightly higher prevalence of thyroid autoimmunity. At baseline it is currently impossible to predict their response to omalizumab.

Introduction

Omalizumab has become an essential treatment for patients with chronic spontaneous urticaria (CSU) unresponsive to antihistamines even at higher than licensed doses (1). Anti-IgE is able to induce a rapid drop in UAS7 levels in about 70% of cases (the so-called early or fast responders) and a slower but equally good response over 3-4 months in further 15% of patients (the so-called late or slow responders; the remaining 15% seem refractory to the treatment (2). Recently, several studies showed a relationship between baseline total IgE levels and the clinical response to the drug (3, 4). With the possible confounding factor of atopic status (5), average baseline total IgE levels are significantly lower in patients unresponsive to omalizumab than in those partially or totally responsive to the drug. The detection of an IgE-mediated, "auto-allergic" pathogenic mechanism in a large proportion of CSU patients represents a reasonable explanation for a rapid response to omalizumab by severely affected patients (6). In contrast, much less clear are the events occurring slow- and non-responders. A recent international, multicenter study (7) was able to identify a specific subset of patients showing several signs of IgG-mediated autoimmunity, including IgG specific for the high affinity IgE receptor (FceRI) or for IgE, which were characterized by low total IgE levels. Nonetheless,

also these subjects might show a good, albeit frequently slow, response to omalizumab in view of the multiple effects of this drug which include among the others a down regulation of high affinity IgE receptor on mast cells and basophils (reviewed in ref. #8). To the best of our knowledge, CSU patients showing a slow response to omalizumab or not responding at all to the drug have not been analyzed vis-a-vis so far. The present study analyzed and compared a series of clinical and serological features in these two subsets of patients with CSU.

Methods

The starting general population was represented by a group of 170 patients with severe CSU (UAS-7 > 30) unresponsive to second generation antihistamines at higher than licensed doses submitted to omalizumab 300 mg/month for at least 3 months. One-hundred-twenty-four patients showed a prompt response to the drug (*i.e.*, a drop of UAS-7 > 50% one month after the first administration) and were excluded from the study. Sixty-three randomly selected subjects from this group were used as control group. The remaining 46 patients (M/F 13/33) who did not show any response 1 month after the first administration were studied. Based on their subsequent response to omalizumab, which was assessed one month after the third administration, patients were classified as late responders (showing a drop > 50% of baseline UAS-7 levels; n = 23) or unresponsive (no change in urticaria activity; n = 23). The need to evaluate patients after 3 administrations comes from the current Italian legislation that forbids to continue omalizumab administration beyond 3 months in the absence of any response. The two subgroups were compared for age, sex, disease duration, and for a series of baseline laboratory parameters including ESR, CRP, thyroid autoimmunity, total IgE, D-dimer, and atopic status. Atopic status was detected by SPT with a large panel of commercial extracts of both seasonal and perennial respiratory allergens (Allergopharma, Reinbeck, Germany) that were carried out and read following established methods (9). The chi-square test with Yates' correction, the two-tailed Student's t-test, or the Mann-Whitney non-parametric test were employed to compare the two study groups where appropriate. Probability values < 5% were considered statistically significant. The study was approved by the internal review board, and all the patients signed an informed consent to use their clinical data in an anonymous form.

Results

Table I summarizes the findings in the two study groups and in the control group. The two subsets did not differ in gender, age, disease duration, prevalence of elevated CRP, ESR, D-dimer, thyroid autoimmunity, and total IgE levels. Further, no patient in the two groups showed sign of co-existing inducible urticaria. Patients unresponsive to omalizumab showed a 3 times higher prevalence of thyroid autoimmunity than late responders (9/21 [42%] *vs* 3/22 [14%]; NS). In contrast, atopic status was more frequent among late responders (9/23 [39%] *vs* 2/23 [9%]; p < 0.05). Notably, the control group (*i.e.*, the early omalizumab responders) showed a prevalence of atopic status and of thyroid autoimmunity that was more similar to late responders than to non-responders.

Total IgE levels were well below the normal range (*i.e.*, < 50 UI/ml; normal cut-off level 100 UI/ml) in the large majority of patients (23/34 [68%]) with an equal distribution between non-responders (14/18 [77%]) and slow responders (9/16 [56%]). Median total IgE levels were 42 UI/ml (5 – 1000) and 9 UI/ml (1-264) in late responders and non-responders, respec-

Table I *- Comparison between the baseline clinical and serological characteristics of the study populations.*

	Late responders (n = 23)	**Non responders (n = 23)**	**p**	**Controls (Early responders) (n = 63)**
Age (median and range)	53 (12-78)	54 (16-77)	NS	52 (13-89)
Sex (M/F)	9/14	4/19	NS	31/32
Median Disease Duration (mo)	10 (2-300)	9 (2-500)	NS	9 (2-600)
Positive CRP	4 (20%)	7 (30%)	NS	10 (16%)
Positive ESR	3 (19%)	6 (27%)	NS	2 (3%)
Atopic status (%)	9 (41%)	2 (9%)	< 0.05	21 (33%)
Median total IgE (UI/ml)	42 (5 – 1000)	9 (1-264)	NS	184 (16-1139)
Elevated D-dimer	11/22 (50%)	12/21 (57%)	NS	22/51 (43%)
Median D-dimer (ng/ml)	493 (159-2455)	658 (190-2500)	NS	487 (160-3700)
Thyroid autoimmunity	3/22 (14%)	9/21 (42%)	NS	12/57 (21%)

tively. The difference, albeit clear, did not reach the statistical significance. In contrast, the control group showed a much higher level of baseline total IgE than both study groups. In total, 7 patients showed total IgE levels exceeding 100 UI/ml; of these, 5 were atopic: 2/2 in the non-responders group and 3/5 in the slow responders group. After the exclusion of atopic patients, the maximum value of total IgE recorded among non-responders was 67 UI/ml, whereas among late responders values ranged between 5 IU/ml and 442 IU/ml.

Discussion

This is the first study comparing two minority subgroups of patients with severe CSU identified by their response to anti-IgE therapy, namely those unresponsive and those showing a slow response to omalizumab 300 mg/month for 3 months. Taken together, these two subgroups represent about 30% of patients with severe CSU undergoing anti-IgE treatment. It must be admitted that the present study might show a partial classification bias. In fact, in some cases the response to omalizumab may become clinically apparent after more than 3 months of treatment; unfortunately, the current Italian legislation does not allow pursuing the treatment beyond 3 months in the absence of any appreciable clinical benefit. Therefore, it is possible that some patients that were eventually included among non-responders were in effect very slow omalizumab responders. Another possible bias is that some patients might have responded to higher doses of omalizumab (10). However, again the current Italian rules do not allow increasing the dosage of omalizumab in the absence of a clinical response at 300 mg/month. Also in this case it is possible that some omalizumab responders were mistakenly classified as non-responders. However, in previous studies updosing of omalizumab was mostly successful in subjects showing a partial response at 300 mg/month, which was not the case in the patients studied here.

The most interesting finding of this study is the similarity between these two subgroups of urticaria patients in terms of both clinical and serological features. Non-responders showed a higher prevalence of thyroid autoimmunity, although this was statistically non-significant). Interestingly, there was a higher prevalence of atopic patients among late omalizumab responders, which is a novel finding. This might partially explain the different outcome, since omalizumab in atopic subjects might have enough IgEs to bind to produce a non-specific downstream effect in FceRI-bearing cells to which urticaria patients could partially benefit from. In effect late responder patients were quite similar to the control group (*i.e.*, early omalizumab responders) in terms of both atopic status and thyroid autoimmunity. With the exception of atopic subjects, most patients in the two groups showed very low total IgE levels, which is in keeping with the observed association between elevated IgE levels and a rapid response to anti-IgE treatment in CSU (3, 4, 11). In effect, in a recent study comparing CSU patients showing a rapid or a low response to omalizumab the former showed a much higher prevalence of elevated total IgE (12). Both groups studied here resembled those CSU patients with several signs of IgG-mediated autoimmunity investigated in the PURIST study, who also showed low total IgE levels and a high prevalence of thyroid autoimmunity (7). Of course, possible differences between the two groups in parameters that were not considered here cannot be ruled out. For instance, it would have been interesting to perform a basophil activation test or the measurement of FceRI, but these methods were not routinely available.

A rapid response to omalizumab occurs in the majority of patients with severe CSU, possibly as the result of the blockade of autoreactive IgE (both circulating and bound to the high affinity IgE receptor on effector cells) by IgG-anti-IgE antibodies (6, 8). The events leading to a slow response or to the non-response to the drug are less clear. In patients showing low total IgE levels and an IgG-mediated autoimmune process able to activate mast cells and basophils via the high affinity IgE receptor, either directly (by IgG-anti-FceRI) or indirectly (by IgG directed against receptor-bound IgE) (13, 14), the effect of omalizumab might rely on the down-regulation of IgE receptors, a process that would take some months of treatment to occur (8). Of course, other mechanisms might also play a role in these subjects, including a reduction in mast cell releasability, an improvement of basophil IgE receptor function, or a reduction of the activity of intrinsically 'abnormal' IgE (8). In non-atopic patients showing elevated IgE, a slow response to the drug might be due to the contemporary presence of IgE and IgG-mediated autoimmunity (15). In contrast, the complete absence of response to omalizumab might suggest a pathogenesis that does not involve at all (*i.e.*, bypasses) the high affinity IgE receptor. In effect, some studies demonstrated the presence of circulating, low molecular weight histamine releasing factors able to induce the degranulation of a human mast cell line missing the FceRI receptor in the sera of CSU patients (16, 17). Further, Ertas and co-workers, following-up their CSU patients treated with omalizumab found that in non-responders the drug administration did not cause any increase in total IgE levels (4), which is a common finding in patients treated with this drug.

Conclusions

In conclusion, slow and non-responders to omalizumab 300 mg/month show impressive clinical and serological similarities, including low total IgE levels. Therefore, it is currently not possible to predict whether patients with severe CSU and low IgE levels will show a slow response or will not respond to anti-IgE treatment.

Conflict of interests

The author declares that he has no conflict of interests.

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ORIGINAL ARTICLE | Eur Ann Allergy Clin Immunol | Vol 53, N.6, 267-276, 2021

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Opinions of patients with persistent asthma regarding the use of mobile applications for disease monitoring

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Key words

Asthma; medication adherence; mobile applications; cell phone use; smartphone.

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Doi
10.23822/EurAnnACI.1764-1489.175

Summary

Background*. We assessed adherence to treatment and management needs of adults with persistent asthma and their interest in using apps for asthma management. Secondarily, we explored patients' opinions about an app to assess and improve adherence to treatment.* ***Methods.*** *A cross-sectional study was conducted with 40 adults with persistent asthma (49.9 ± 15.8 years) recruited at outpatient clinics from a district hospital. Participants answered a survey on sociodemographic, asthma control, treatment adherence and use of mobile devices, social networks and apps. Four patients participated in a prospective extension of the study, in which they were invited to use the InspirerMundi app.* ***Results****. 48% of the participants had at least ≥ 1 exacerbation in the previous year and 85% had uncontrolled asthma. Self-reported adherence to treatment showed that one in four participants had low adherence. At least daily, 55% of participants navigated on the internet with their smartphone/tablet, 35% used apps and 93% social networks. Nine (22%) participants had previously used health/fitness apps and 65% would like to use apps to improve inhaler adherence.* ***Conclusions.*** *Most participants had uncontrolled asthma, reported high adherence to treatment and were daily users of social networks and the internet. Only 1/4 used apps but 2/3 would like to use apps to support asthma management.*

Impact statement

Two-thirds of the participants with access to mobile devices would like to use an app to improve monitoring and adherence to treatment.

Introduction

Asthma affects around 235 million people worldwide (1). Regular disease monitoring and its proper management may allow a normal life (1, 2). Inhaler controller medications are the cornerstone of effective asthma treatment. However, there is low adherence to medication in patients with asthma, which leads to worse outcomes and higher disease burden (3-5).

One of the main factors contributing to the difficulty in adhering to asthma treatment is poor patients' perception of asthma, since asthma attacks are episodic, which may constitute a barrier to understanding the need of control medication (6, 7). There is a need to improve our understanding of the patterns of adherence to inhaled controller medications and to identify the specific reasons for non-adherence and other needs among patients with persistent asthma. It is also important to develop patient-centred solutions, allowing patients to be actively involved in the control of their asthma, through the implementation of self-monitoring strategies (8).

Interactive asthma monitoring tools, through the use of internet-based and social media solutions, have been associated with better outcomes in patients with asthma (9). A simple daily text message reminder was associated with increased adherence to treatment (10). In addition, most patients with asthma show a preference for using internet applications for future self-monitoring (11). However, it is important to improve our understanding of the preferences, interest and usage of web-based strategies in daily routine of people with persistent asthma, to improve adherence to treatment.

Apps can be a feasible solution, since they can be used at any time, are easily integrated into daily life, can combine mechanisms to determine treatment adherence, interactive communication and gamification that can influence patients' behaviour changes (12). In fact, the use of mobile applications made patients feel that their health care continued even outside the hospital (11). It is therefore hypothesised that an app, with gamification and peer-support elements, may improve adherence to treatment in patients with asthma. However, usefulness and acceptability by end users need to be assessed in a real-world study.

The main aims of this study were to evaluate adherence to treatment and management needs of adults with persistent asthma; to assess their interest in using apps for management and adherence to treatment, and to describe the use of mobile devices, social networks and apps. The secondary aim was to investigate users' opinions about an app to assess and improve adherence to treatment.

Materials and methods

Study design and participants

A cross-sectional study with 40 adults with asthma and a pilot extension study with four of those patients were performed. Patients were recruited during 120 appointment periods of allergy and pulmonology outpatient clinics of Hospital Pêro da Covilhã, between September 2017 and June 2018. Patients were included if they had persistent asthma, were ≥ 18 years old, had an active prescription of inhaled controlled medication and had access to mobile devices (smartphone/tablet). Patients with a diagnosis of other chronic conditions with possible interference with the study aims were excluded. In the prospective extension study, patients had additionally to answer positively to the question about interest in using apps to improve inhaler adherence. All participants were informed about the study and written informed consent was obtained prior to data collection. The Ethics Committee of Hospital Pêro da Covilhã approved the study.

Data collection

First, sociodemographic and clinical (smoking habits, body mass index-BMI, age of asthma diagnosis, asthma self-monitoring and written asthma treatment plan) data were collected. To assess management needs, patients' asthma control, exacerbations and use of health care resources were collected. Clinicians reported patients' asthma clinical characteristics and control according to Global Initiative for Asthma (GINA) (13). Patients completed the Control of Allergic Rhinitis and Asthma Test (CARAT) (14). CARAT total (CARAT-T, 0-30), upper airways (CARAT-UA, 0-12) and lower airways (CARAT-LA, 0-18) scores were calculated. Scores > 24 on CARAT-T and ≥ 16 on CARAT-LA defined good disease control. Number of exacerbations (defined as episodes of progressive increase in shortness of breath, cough, wheezing, and/or chest tightness, requiring change in maintenance therapy (15), treatment with oral corticosteroids, days of work/school lost due to routine medical visits, unscheduled medical visits, hospitalizations and days of work/school lost due to asthma attacks in previous year were also assessed.

To assess inhaler adherence, patients answered the 4-item Morisky Medication Adherence Scale (MMAS-4) (16, 17). The scores range from 0 to 4 (0 indicates high adherence, 1-2 medium adherence and 3-4 low adherence). In addition, patients assessed their global adherence to inhaled controller medication for asthma during the previous week ("how would you classify your adherence to your daily inhaler during the last week?") using a Visual Analogic Scale (VAS), ranging from 0 (worst) to 100 (best) millimetres (18). Satisfaction with inhaler was assessed through a questionnaire previously used in patients with asthma (19). This questionnaire includes 4 VAS (0 worst - 100 best) questions, which evaluate patients self-perception of inhaler technique ("I perform correctly the technique of my inhaler"), satisfaction with the inhaler device ("I feel satisfied with my inhaler"), comfort with public use of the inhaler ("I feel comfortable using my inhaler in public") and perception of how his/her preferences were taken into account at the time

of inhaler's prescription ("I feel that my physician took into account my opinion and preferences when choosing my inhaler") (19). Then, the participants completed the specific Beliefs about Medicines Questionnaire (BMQ-Specific) (20). The BMQ-Specific includes a 5-item Necessity scale (score 5-25) and a 6-item Concerns scale (score 6-30). Higher scores represent greater patient's beliefs in the represented concept.

Finally, participants filled in the Smartphone Usage Scale and the General Social Media Usage Subscale of the Media and Technology Usage and Attitudes Scale (MTUAS) (21). Patients were also asked about previous use of health/fitness apps and asthma apps, if they would like to use apps to manage their asthma and, and if they would like to use apps to improve inhaler adherence.

In the prospective extension study, four patients installed the InspirerMundi app on their mobile devices and were invited to use the app daily for 6 months. At the end of this time period, patients were interviewed by phone to answer a survey about the app. The survey included questions regarding satisfaction with each of the app components; suggested app improvements and also the System Usability Scale (SUS) (22). SUS score range from 0 to 100, and scores > 68 mean good system usability.

InspirerMundi App

InspirerMundi aims to transform adherence to treatment into a positive experience through immediate and enjoyable feedback (gamification), while allowing for verified inhaler adherence monitoring (12). The app, available for iOS and Android, integrates 3 main components: monitoring, gaming, and social/peer support. In the monitoring component, users can add their current medications and record performed inhalations using the image-based inhaler adherence detection tool. The mobile app allows patients to view statistics on the adherence to medications and gives alerts of scheduled medication. Patients can also record relief medication use, asthma-related symptoms and exacerbations, and can share data with their physician. In the gaming component, the aim is to increase the sphere of influence by the network of Inspirers and Warriors. The app engages patients with a customisable "Warrior" (beginner player), which can become an Inspirer (advanced player) that gives support to his/her Warriors. Points are given when users take their medication according to plan. In the social/peer support component, users can share and demonstrate their points/badges and achieve social recognition; exchange messages and alert their warriors regarding missing medication doses.

Statistical analysis

Statistical analyses were conducted with IBM SPSS Statistics v21 (Chicago, US). Categorical variables were described with absolute and relative frequencies and continuous variables with mean and standard deviation or median with interquartile range, according to data distribution. Differences between patients with or without interest in using apps were tested using the χ^2 test for categorical variables and Mann-Whitney U Test for continuous variables. Logistic regression analysis was used to explain the interest in using asthma apps. Adjusted odds ratio (OR) with 95% confidence interval (95% CI) were calculated. All variables possibly related to interest in using apps were considered. The level of significance was $\alpha < 0.05$.

Results

Participants

Forty patients (31 females) with a mean age of 49.9 ± 15.8 years participated. Most were married, had an education level ≥ 10 years and were employed. Almost two thirds of the participants had never smoked. An association between interest in using apps for asthma and age, marital/civil status, education level and BMI was observed (**table I**).

Treatment adherence and management needs

The mean age at asthma diagnosis was 29.6 ± 15.6 years. According to CARAT, 85% (n = 34) of the participants had uncontrolled disease (75% considering solely the lower airways) and almost half had exacerbations in the previous year. Yet, almost none had lost a work/school day due to asthma attacks. A relation between interest in using mobile applications for asthma and age of asthma diagnosis was observed (**table II**). The BMQ necessity score had a mean of 19.1 ± 3.3 and the BMQ concern score a mean of 15.6 ± 3.9. In terms of the 4-MMAS, most patients (55%) had medium adherence to treatment, and one fifth had high adherence. Most participants had at least one problem regarding adherence to treatment and most patients (68%) forgot to take their medication (**figure 1**). Self-perception of adherence to inhalers in the previous week was high (median 91%) as were self-evaluation of inhaler technique (median 99%), satisfaction with the inhaler device (median 99%), patient's perceived involvement in the choice of the device(s) (median 98%) and public use of the inhaler (median 100%). Association between interest in using apps for asthma and self-perception of adherence to inhalers in the previous week, self-evaluation of inhaler technique, patient's perceived involvement in the choice of the device(s) and public use of the inhalers was observed (**table II**).

Participants mostly browsed the web, searched for information and used apps on their smartphone (**figure 2**). Those who used their smartphone/tablet more also showed greater interest in using apps. A relationship between interest in using mobile applications for asthma and browsing the web, listening to music, recording video, using apps, searching for information and checking Facebook page was observed. Most (93%) participants used Facebook, 22% used apps of health/fitness and only one participant had used an app for asthma (**figure 3**). However, most patients (65%) would like to use apps to improve adherence to treatment.

Table I *- Characteristics of the participants.*

Characteristics	Without interest (n = 18)	With interest (n = 22)	Total (n = 40)
Age, mean ± SD (range) years	59.6 ± 11.1	41.9 ± 14.8*	49.9 ± 15.8 (20-77)
Female, n (%)	12 (67)	19 (87)	31 (78)
Marital/Civil Status, n (%)			
Married/ Civil union	16 (89)	12 (55)*	28 (70)
Singled/Divorced	2 (11)	10 (46)*	12 (30)
Education level, n (%)			
< 10 years	13 (72)	4 (18)*	17 (43)
≥ 10 years	5 (28)	18 (82)*	23 (57)
Employment, n (%)			
Employed	7 (39)	14 (64)	21 (53)
Retired	8 (44)	2 (9)	10 (25)
Unemployed/Not working due to poor health	3 (17)	1 (3)	5 (13)
Student	0	3 (8)	3 (8)
BMI, mean±SD (range) kg/m^2	27.9 ± 2.6	25 ± 4.7*	26.3 ± 4.1 (18.5-35.1)
Smoking status, n (%)			
Non-Smokers	12 (67)	13 (59)	25 (63)
Ex-smoker	4 (22)	6 (27)	10 (25)
Current smoker	2 (11)	3 (14)	5 (12)
Passive smoking, n (%)	5 (28)	12 (55)	17 (43)

BMI: Body Mass Index; *p < 0.05.

The logistic regression model was statistically significant (χ^2 = 21.284, p < 0.001) and explained 59% (Nagelkerke R^2) of the interest in use apps for asthma. The variables use of apps (OR = 28.3; 95% CI 2.1-374.9) and the frequency of Facebook use (OR = 2.3; 95% CI 1.1-4.7) were the independent variables.

Pilot study

Four participants (1 male, 20-46 years; ≥ 10 education years) tested the InspirerMundi app. The SUS score was 65 for one participant and > 68 for the other participants (80, 82.5, 85). Concerning the monitoring component, three patients were completely satisfied/satisfied and one had no opinion. Regarding the inhaler usage detection tool, two participants were completely satisfied/satisfied and the other two had no opinion. Regarding the app gamification, two were satisfied, one had no opinion and one was unsatisfied. As for the app social network, two were completely satisfied/satisfied, one had no opinion and one was unsatisfied. All participants were globally satisfied with the app and all would recommend it to others. One participant considered that the use of the app increased his/her awareness of the importance of adherence to medication and two stated that the app increased their motivation to adhere to it. Participants stated that the app allowed them to better control the time/doses of the medication; to register their symptoms and to have greater perception of control of their symptoms. Two participants considered that the game component should be more engaging, while another participant considered that the app stalled several times. They suggested simplifying the record of inhaled medication and the main screen presentation, with three menus: medication, CARAT and weekly/daily symptoms.

Discussion

This study contributes to the much needed knowledge about adherence to treatment, asthma management problems and about opinions on the use of apps in patients with asthma. A main finding was that two thirds of the participants with access to mobile devices would like to use apps for asthma to improve monitoring and adherence to treatment. Furthermore, insufficient control of asthma, poor monitoring between medical

Table II *- Asthma control and patients' beliefs, adherence and preferences regarding inhalers.*

Variables	Without interest (n = 18)	With interest (n = 22)	Total (n = 40)
Age of asthma diagnosis, mean ± SD (range) years	37 ± 12.9	23.5 ± 15.1*	29.6 ± 15.6 (1-55)
Number of different inhalers, n (%)			
1	7 (39)	3 (14)	9 (23)
2	8 (44)	17 (77)	26 (65)
3	3 (17)	2 (9)	5 (12)
GINA classification of asthma control n (%)			
Well controlled	6 (33)	11 (50)	17 (43)
Partly controllled	7 (39)	5 (23)	12 (30)
Uncontrolled	5 (28)	6 (27)	11 (27)
CARAT, mean ± SD (range)	19.9 ± 6.7	17 ± 8.4	17.9 ± 7.7 (0-29)
CARAT, n (%)			
Controlled (> 24)	2 (11)	4 (18)	6 (15)
Not controlled	16 (89)	18 (82)	34 (85)
CARAT Upper Airways	7.2 ± 3,0	5.7 ± 3.6	6.4 ± 3.4
CARAT Lower Airways	11.7 ± 5.9	11.3 ± 5.8	11.5 ± 5.8
Asthma self-monitoring, n (%)	1 (6)	4 (18)	5 (13)
Days of work/school lost due to routine medical visits past 12 months, n (%)			
0	16 (89)	17 (77)	33 (83)
1-4	2 (11)	5 (23)	7 (17)
Clinician explain how to use the inhaler past 12 months, n (%)	16 (89)	20 (91)	36 (90)
Asthma written treatment plan, n (%)	15 (83)	19 (86)	34 (85)
Exacerbations past 12 months, n (%)			
0	11 (61)	10 (46)	21 (53)
1-2	7 (39)	9 (40)	16 (40)
≥ 3	0 (0)	3 (14)	3 (7)
Treatment with oral corticosteroids past 12 months, n (%)	7 (39)	8 (36)	15 (38)
Asthma unscheduled medical care past 12 months, n (%)			
Emergency department visits past 12 months	5 (28)	5 (23)	11 (27)
Hospital admissions past 12 months	1 (6)	0	1 (3)
Days of work/school lost due to asthma attacks past 12 months, n (%)			
0	17 (94)	21 (96)	39 (98)
≥ 1	1 (6)	1 (5)	1 (2)
BMQ necessity, mean ± SD (range)	19.6 ± 2.1	18.7 ± 3.9	19.1 ± 3.3 (8-25)
BMQ concern, mean ± SD (range)	15.6 ± 2.2	15.5 ± 4.8	15.6 ± 3.9 (6-27)
4-MMAS, n (%)			
High adherence	4 (22)	4 (18)	8 (20)
Medium adherence	9 (50)	13 (59)	22 (55)
Low adherence	4 (22)	5 (23)	9 (22)

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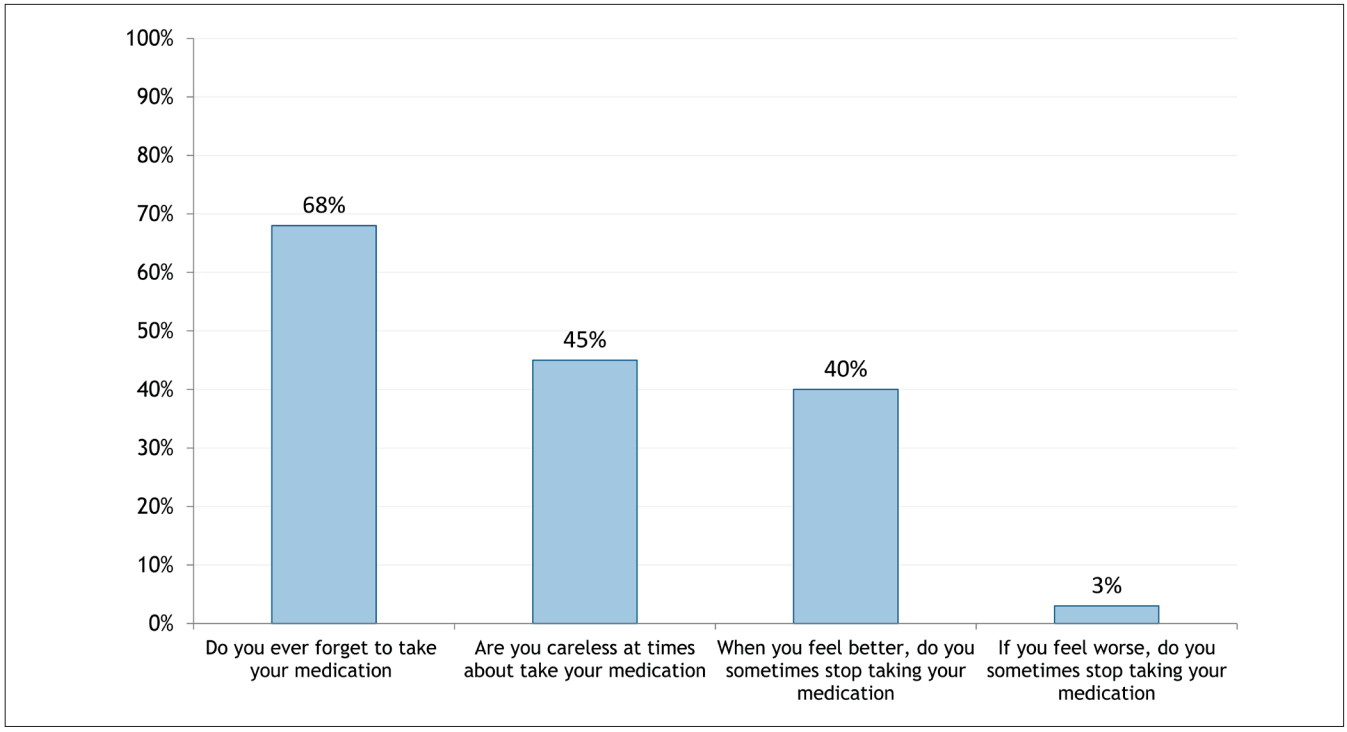
Variables	Without interest (n = 18)	With interest (n = 22)	Total (n = 40)
Adherence to inhalers last week[a], Median (P25-P75)	100 (83-100)	83 (71-98)*	91 (74-100)
Preferences[a], Median (P25-P75)			
I perform correctly the technique of my inhaler	100 (97-100)	97 (98-100)*	99 (92-100)
I feel satisfied with my inhaler	100 (90-100)	98 (94-100)	99 (94-100)
I feel that my physician took into account my opinion and preferences when choosing my inhaler	100 (95-100)	93 (49-100)*	98 (67-100)
I feel comfortable using my inhaler in public	100 (99-100)	96 (90-100)*	100 (94-100)

GINA: Global Initiative for Asthma; CARAT: Control of Allergic Rhinitis and Asthma Test; *p < 0.05; BMQ: the Beliefs about Medicines Questionnaire; 4-MMAS: Morisky 4-item Medication Adherence Scale; [a]Visual analogic scale; range 0-100 (best).

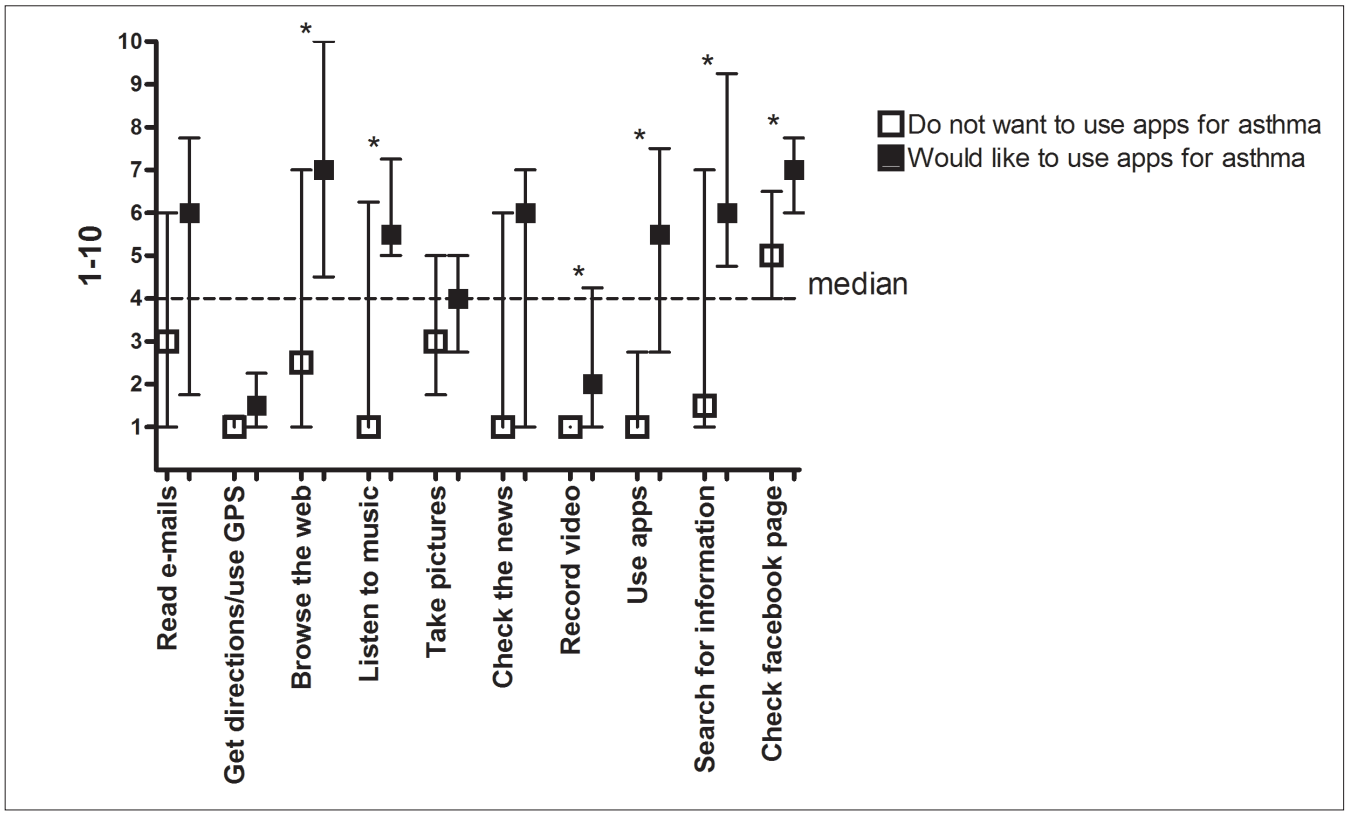
Figure 1 *- 4-item Morisky Medication Adherence Scale.*



appointments and a possible overestimation of the participants regarding treatment related perceptions were observed.

The main management needs identified were the high proportion of patients with insufficient asthma control, the lack of self-monitoring between medical visits and the mismatch between clinical outcomes and patients' perceptions about their management. Near half of the patients had an asthma exacerbation in the previous year; however, patients reported very few days of missed work/school and very high levels of written treatment plans. In addition, perceptions of their adherence and inhaler technique were also very high. Therefore, there is a disassociation between patients' perceptions and clinical outcomes. Most of the participants reported a high satisfaction with the inhaler device, were confident about the correctness of their inhaler technique and about using their inhaler in public and considered being involved by the physician in the choice of the device. Our results on inhaler technique are apparently much better than those obtained by Chorão *et al.* (19), but this difference may reflect the different methods used. In the

Figure 2 *- Smartphone usage scale (9 items) and General social media usage subscale (1 item) of Media and Technology Usage and Attitudes Scale.*

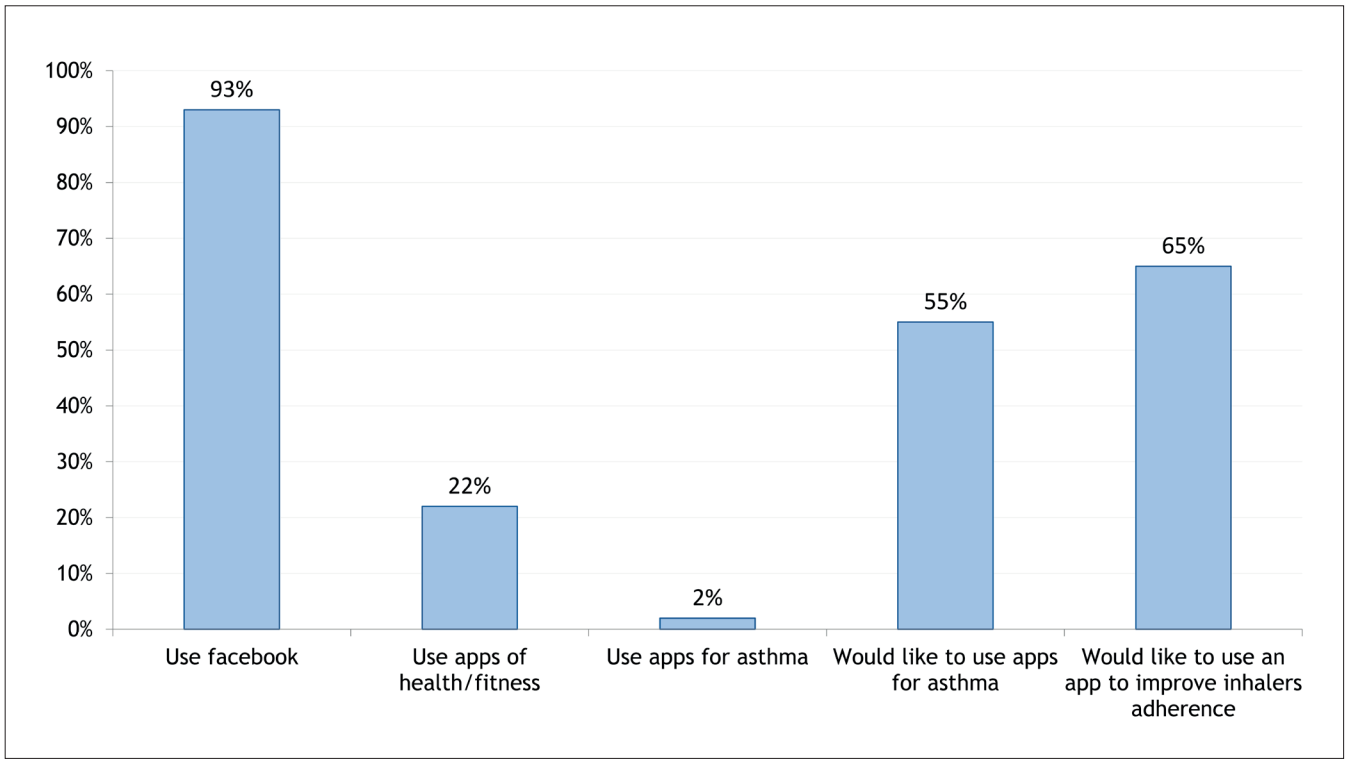


study by Chorão *et al.*, the inhaler technique was observed by the researcher and included patients with asthma and with chronic obstructive pulmonary disease (19). Thus, opinions and preferences of patients concerning their inhaler device may be over-estimated. One of the most relevant management needs may be to improve patients' awareness of the importance of inhaler technique, adherence and involvement in treatment decisions. In fact, overestimation of disease control by patients was apparent in a study by Sá-Sousa *et al.* (23), in which 88% of patients with uncontrolled asthma considered their asthma to be under control.

The majority of participants had uncontrolled asthma, with CARAT scores similar to those observed in other studies. A similar situation was also observed in both elderly and non-elderly asthmatic patients from the region of Beira Interior (24). A study carried out in 224 participants recruited in pharmacies located in the same district of this study obtained similar results of CARAT (mean 17.8; 87% uncontrolled asthma) (25). In another study, involving 200 patients with a mean age of 33.6 ± 12.3 years, of which 86 had allergic rhinitis and asthma, 86% had uncontrolled asthma (26). There is a high percentage of patients with uncontrolled asthma, which is a cause for concern and calls for measures to be taken to improve these outcomes. The availability and use of tools to support asthma self-monitoring may be one of the measures to improve asthma management.

We observed high values of treatment with oral corticosteroids in the previous year (38%) and visits to the emergency department (27%), and relatively few hospitalisations (3%). A study by Price *et al.*, with 8000 patients with asthma from 11 European countries showed similar results in the percentage of treatment with oral corticosteroids (44%) and of emergency department visits (24%), but reported more hospitalisations (12%) (27). These differences may be explained by the fact that in the European study, participants were recruited by an online survey which means that a broader spectrum of patients was represented, whereas in the present study participants were regularly followed up by a clinician at secondary care. It was observed that in the present study, according to GINA, 43% of the participants had well controlled asthma and, according to 4-MMAS, approximately half of them had medium adherence to treatment while in the European study only 20% had well controlled asthma and many with

Figure 3 *- Use of social networks and apps and interest in using apps for asthma.*



low adherence to therapy. In our case this factor may contribute towards reducing hospitalizations but adherence to treatment remains an important issue and we need objective data to confirm the high levels of self-reported adherence observed.

The mean scores for the Necessity and Concerns subscales are comparable to the study by Salgado *et al.*, carried out in 300 outpatients of several illness groups (19.9 for Necessity and 17.7 for Concerns), which indicates that patients with asthma perceive necessity and concerns similarly to patients with other chronic diseases (20). The BMQ results are associated with poor medication adherence and highlight the importance of addressing patients concerns during medical visits.

Mobile devices can be an instrument that helps asthma self-monitoring because they are part of people's daily lives, allow the users to request data wherever they are, allow more timely health monitoring and can associate personal and social contact (28). We verified that most of the participants used Facebook daily and that browsing the web, searching for information and using apps were daily used on their smartphone. We observed that one third of the participants had already used apps of health/fitness and despite the fact that only one participant had used an app for asthma, more than half of the patients showed interest in using apps to improve inhaler adherence. Fonseca *et al.* reported that patients with moderate-to-severe asthma and with access to mobile phones had interest in using it for self-monitoring asthma (91%) and for information about medication (88%) (29). The designs of the studies and the 14-year difference in data collection do not allow direct comparisons, but there may be differences in the interest of patients in using apps for different asthma related purposes. As apps become instrumental in providing health care measures, further research is needed to prove the importance of these tools. In addition, it is believed that the development of apps grounded in research will probably have a role in increasing patients' interest in using these tools.

As an early pilot study, four patients reported on the use of the InspirerMundi app. The participants liked the app and reported that it allows them to have better understanding of the medication/symptoms. The gamification and the social network were the components with less positive opinions from the users, but all components need to be improved in app future versions. Also, more studies with larger samples are needed to further evaluate the app feasibility and validity.

This study has some limitations. First, the selection bias related to the inclusion criterion of having access to mobile devic-

es, since the site of recruitment has a high proportion of older patients. Another limitation is the small sample size, especially of the pilot study. Nevertheless, we report relevant information regarding asthma management issues and new approaches to improve them. Third, adherence was assessed using subjective measures (4-MMAS and VAS), which are known to overestimate of real adherence. Future studies should combine subjective and objective measures of adherence. A fourth limitation involves the fact that most patients had self-management asthma plans and their inhalation technique was regularly checked, a situation which is not often found in other settings where patients are seen and which may hinder generalization. Future studies will need to recruit a larger sample with participants from several healthcare units with greater socio-economic and clinical variety.

Conclusions

Two-thirds of the participants with access to mobile devices would like to use an app to improve monitoring and adherence to treatment. Participants had a high daily usage of their mobile devices, and social networks but only one third used other apps. The self-reported measures about treatment adherence and perceptions had high scores which contrast with poor asthma control. Improvements in self-monitoring between medical appointments are asthma management needs that are apparent from this study and apps can be important tools.

Contributors

C.C., L.T.B., C.J. and J.A.F. designed the research, C.C., L.T.B., S.V. and J.F. collected data, C.C. and C.J. analyzed data, C.C. wrote the paper, and all authors reviewed and approved the final version of the manuscript.

Acknowledgments

We would like to acknowledge the patients for their participation in this study. We would like to acknowledge Mundipharma-Portugal for funding the dissemination of the InspirerMundi app.

Conflict of interests

The authors declare that they have no conflict of interests.

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A case of severe allergic eosinophilic asthma with nasal polyposis in a patient affected by Birt-Hogg-Dubé syndrome successfully treated with benralizumab

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Key words

Birt-Hogg-Dubé; severe asthma; pneumothorax; benralizumab; eosinophilic asthma.

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Doi
10.23822/EurAnnACI.1764-1489.222

Summary

Birt-Hogg-Dubé (BHD) syndrome is a rare genetic pathology characterized by cutaneous fibrofolliculomas, pulmonary cysts and kidney tumours (1). Severe asthma is the most serious form of asthma which does not respond to standard treatments (2). We present the case of a 68 years old male patient who had frequent respiratory tract infections, shortness of breath and decline in lung function, nasal polyposis and hypertrophy of the nasal turbinates, for this reason he was treated as a severe asthmatic patient for several years with ICS + LABA and with high doses of OCS. When we tried to reduce OCS, the patient's symptoms worsened, so we requested a HRTC scan that showed the presence of several cysts spread ubiquitously. The patient had a family history of pneumothorax, for this reason we requested a genetic test that resulted in a heterozygous point mutation on exon 12 (c.1429 C > T) of FLCN gene (3). Despite the diagnosis of BHD syndrome, the patient's clinical condition kept on, suggesting an underlying severe asthma and the blood tests we requested pointed out an high percentage of eosinophils. For this reason, we opted for the administration of benralizumab (4, 5) which resulted in an excellent asthma control and in an increased quality of life.

Impact statement

Other comorbidities can often be hidden in patients with severe asthma as in our case, which is why patients need to be studied to further improve their clinical condition and quality of life.

Introduction

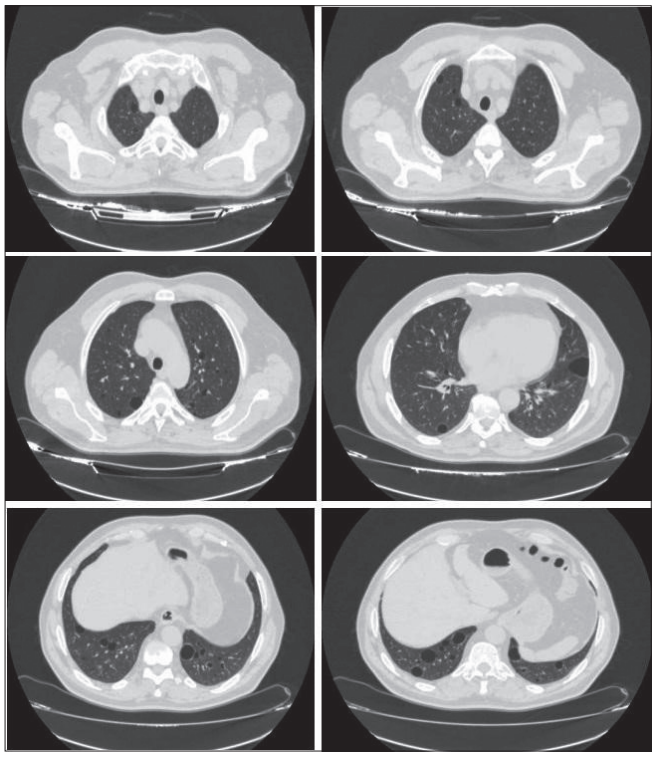
Birt-Hogg-Dubé (BHD) syndrome is an autosomal dominant genetic disorder caused by a mutation in the FLCN gene, which codes for the protein folliculin. The function of the protein is not really clear, but it seems to be a tumor suppressor, with a role in the restriction of the cell growth. It is expressed in the skin, distal nephrons and type I pneumocytes. Patients with BHD syndrome usually have fibrofolliculomas and pulmonary cysts, in a minor percentage of the cases have kidney tumours and spontaneous pneumothorax. Asthma is a chronic respiratory disease characterized by chronic airways inflammation. In the management of the asthmatic patient the goal is to reach disease control assessed by 1) questionnaires (Asthma Control Test (ACT) or Asthma Control Questionnaire (ACQ)) and 2) a recent anamnesis of re-exacerbations. Severe asthma does not respond well to standard treatments. One of the most effective treatments for this life-threatening form of asthma is the biological therapy with humanized anti-immunoglobulin (Ig) (6). Benralizumab is a humanized IgG1k monoclonal antibody that interacts with an extracellular IL-5Rα epitope. It is indicated as an

add-on maintenance treatment in adult patients with inadequately controlled severe eosinophilic asthma despite the high-doses inhaled corticosteroids plus the long-acting β-agonists (5).

Case report

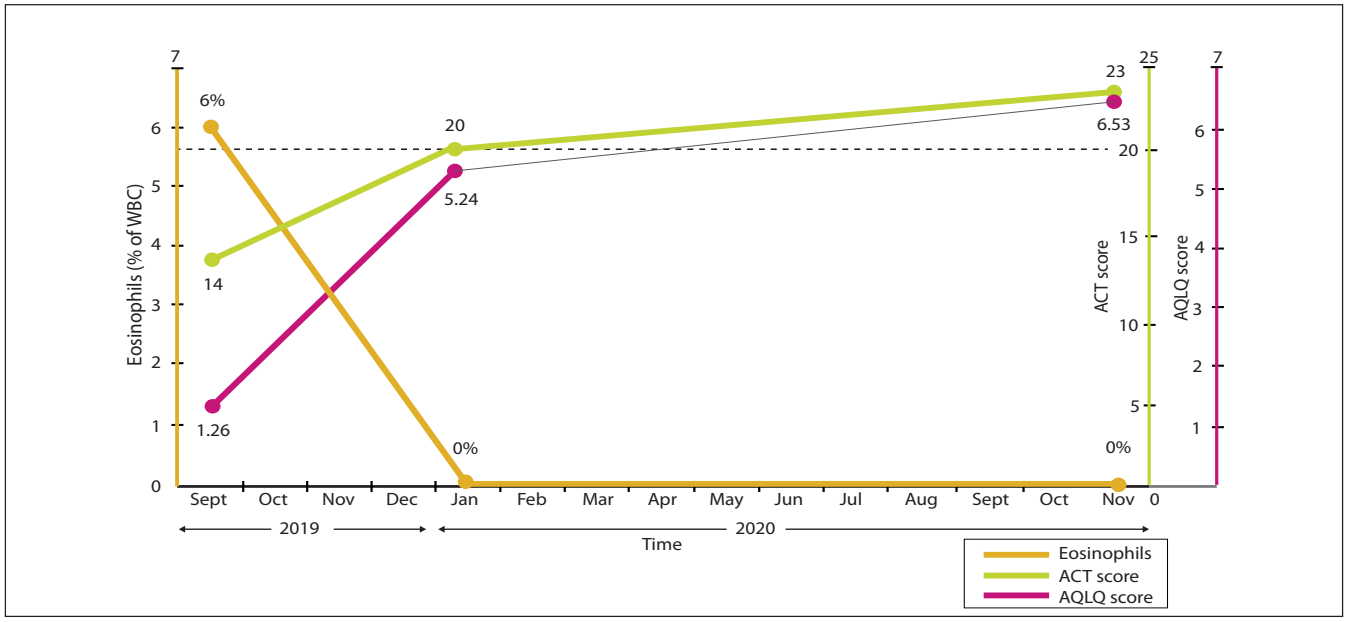
In 2017 came to our attention a 68-year-old never smoker male patient. In anamnesis he had only hypertension in pharmacological treatment, non-controlled atopic asthma and nasal polyposis treated surgically. He referred to our clinic with frequent prolonged respiratory tract infections (including recurrent wheezing attacks) and progressive decline in lung function with shortness of breath and cough. He reported he was treated with ICS + LABA and high doses of oral corticosteroid (OCS) with partial improvement but when he tried to stop or reduce OCS administration, his asthma became poorly controlled because of repeated exacerbation and relapse. The symptoms were suggestive of severe refractory asthma. The spirometric examination resulted in a mild obstruction (FEV1 2.62 - 93%; FVC 3.81 - 103%; FEV1/FVC 69). We requested a HRTC scan that showed us the presence of several cysts, spread ubiquitously, but more frequent at the lung bases (**figure 1**) (7, 8).

Figure 1 *- HRTC scan showed the presence of thin-walled, round and ovoid pulmonary cysts predominating in the lower-medial zones of both lungs.*



We performed a bronchoscopy with BAL that was essentially normal with a value of $CD1^+ < 5\%$. We also performed a dosage of alpha1-antitrypsin that resulted in normal range (150 mg/dl - v.n. 95/175 mg/dl) and a dosage of autoantibodies that didn't show anything significant. Delving into the family history, we discovered that the patient has one brother and two sisters with a history of spontaneous pneumothorax and lung cysts, although our patient hadn't a story of spontaneous pneumothorax. Furthermore, visiting one of the two sisters, we found the presence of fibrofolliculomas on her face, missing in our patient. To confirm the diagnosis of BHD syndrome, we performed a molecular analysis on DNA by direct sequencing of the gene FLCN. The genetic tests, performed on the patient and his sister, showed a heterozygous point mutation on exon 12 (c.1429 C > T) of FLCN gene − already described in a patient affected by BHD syndrome in the literature (3) − with an effect nonsense R477X. Then, we concluded for BHD syndrome, but the patient still kept suffering from shortness of breath, cough and progressive decline in lung function. The patient was also affected by nasal polyposis and hypertrophy of the nasal turbinates, in therapy with intranasal steroid, and experiencing nasal discharge and nasal obstruction. In the blood test we requested, a high percentage of eosinophils in the peripheral blood (6% - 723 cell) was evident. Since comorbidities and non-compliance with treatment were excluded and the inhalation technique was checked, all the criteria for the initiation of biological therapy were fulfilled. Based on the clinical and laboratory data available, we opted for benralizumab, anti-IL-5 antibody, which is indicated as an add-on maintenance treatment in adult patients with severe inadequately controlled eosinophilic asthma, despite the high-dose inhaled corticosteroids plus long-acting β-agonists, as suggested by Bleecker *et al.* (9). After signing an informed consent, we initiated the benralizumab treatment. Consequently, benralizumab has been administered to our patient by subcutaneous injection of 30 mg every 4 week for the first 3 doses and then every 8 weeks thereafter, in addition to the standard therapy. This therapeutic approach resulted in an excellent asthma control (ACT pre-benralizumab 12; ACT post-benralizumab 23; $p < 0.05$), decreased number of respiratory tract infections, suppression of the chronic use of OCS, and increased quality of the patient's life (AQLQ pre-benralizumab 1.26; AQLQ post-benralizumab 6.53; $p < 0.05$). The benefit of this therapy was evaluated every 6 months. After 12 months, the treatment was well-tolerated, and we assessed the effectiveness of this therapeutic modality, and it has been shown to be efficient. We also observed a clear reduction of blood eosinophil counts, which at one year from the beginning of the treatment were 0%. Since no adverse effects have been observed, we decided to continue the treatment with benralizumab up till now. Nowadays, our patient has been on treatment with benralizumab for 14 months, he has no clinical symptoms, with improved spirometry parameters (FEV1 after 6 months 2.75 - 96% and FEV1 after 12 months 2.87 - 99%) and no more exacerbations (**figure 2**).

Figure 2 *- Progress from beginning of benralizumab to November 2020.*



Discussion and conclusions

This case report has two purposes:

1. to focus the attention on a rare disease that should be known by clinicians, especially pulmonologists and thoracic surgeons, in order to avoid diagnostic delays and inappropriate therapies;
2. to centre the attention on the therapy with benralizumab in patients with non-controlled severe asthma that does not respond to high doses of corticosteroids.

Patients with BHD come to our attention for incidental finding to HRTC of cystic lesions or for spontaneous pneumothorax. This is why it's important to know the pathology for the differential diagnosis, while clinicians have to check if patients with non-controlled severe asthma know the indications for the biological therapy. After the therapy with benralizumab, our patient finally controlled its symptoms with an increase of quality of life.

Fundings

Neither financial support nor a grant was received for this study.

Conflict of interests

The authors declare that they have no conflict of interests.

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Eur Ann Allergy Clin Immunol Vol 53, N.6, 280-283, 2021

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Allergic contact dermatitis by ophthalmological medications in Brazil: experience of a dermatology department

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Key words

Allergic contact dermatitis; eye drops; patch test; blepharoconjunctivitis; ophtalmic medications.

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Doi
10.23822/EurAnnACI.1764-1489.190

Summary

Topical treatments in ophthalmologic therapy are significant for the development of allergic contact dermatitis (ACD) in the periorbital region. Preservatives, antibiotics, glucocorticoids, and beta-blocker eye drops are defined as drugs with the highest sensitizing potential. The unavailability of patch test batteries containing substances of ophthalmological use makes it difficult for this diagnosis. In the present report, we describe six patients who developed ACD induced by different agents presenting in eye drops, confirmed with the cutaneous patch tests. The ACD diagnosis due to ophthalmic medications can be challenging, since many different agents can cause it, and the sensitivity of these cutaneous tests is low. Thus, early diagnosis is essential to avoid the complications of ACD on the skin and ocular disorders related to chronic periorbital eczema.

Impact statement

We report six cases of allergic contact dermatitis induced by different agents presenting in eye drops, confirmed with the cutaneous patch tests.

Introduction

Ophthalmic solutions are one significant triggering factor for the occurrence of periorbital contact dermatitis or contact blepharoconjunctivitis (PCD/CBC). There are numerous components such as antibiotics, preservatives of eye preparations, and the active principles as beta-blockers used for glaucoma treatment. The thin thickness of the periorbital epidermis facilitates the permeation of allergens, making this region susceptible to sensitization, consequently resulting in allergic contact dermatitis (1).

Many cases of PCD/CBC are caused by preservatives, especially chloride benzalkonium, sodium chloride, EDTA (Ethylenediamine tetracetic acid), and thimerosal (2). However, according to recent reports in the literature, it was observed that the pharmacologically active substances are also, in large part, triggers with allergic sensitization (2).

The ACD diagnosis due to ophthalmic medications can be challenging as we observed in the literature. First, the unavailability of patch test batteries containing substances of ophthalmological use makes it difficult for this diagnosis. Second, a relatively high false-negative rate in patch testing ophthalmic agents has been reported. Grey *et al*. (3) proposed different hypotheses to explain this phenomenon such as the difference of the thickness by epidermis of the eyelid and the back or arm, sites commonly used for skin patch testing, or the low concentration of hapten in commercial products may not be sufficient to elicit response on traditional patch testing when solely testing the product itself. We describe six patients with ocular diseases conducted by the Ophthalmology and Dermatology services of our institution from January 2018 to January 2020, who presented palpebral or perior-

bital eczema or both. They were diagnosed with Allergic Contact Dermatitis (ACD) induced by the use of ophthalmic medications.

Case series

Between 2018 and 2020, six patients were referred to our service by the Ophthalmology Department because they noticed chronic periorbital pruritus and the presence of periorbital eczema. These patients underwent follow-up for eye diseases, such as glaucoma and cataract, making use of several eye drops to treat these ocular diseases.

Among the patients, four were female, two males, with an average age of 64 years (most patients older than 70 years). At first, on a dermatological examination, all presented erythema, papules, and scaly on the periorbital region and complained of local itching. Five of them had glaucoma and were under specific treatment with eye drops (**table I** and **figure 1**). None of the patients had a personal history of atopic diathesis (dermatitis, rhinitis or asthma).

Patch Test and diagnostic approach

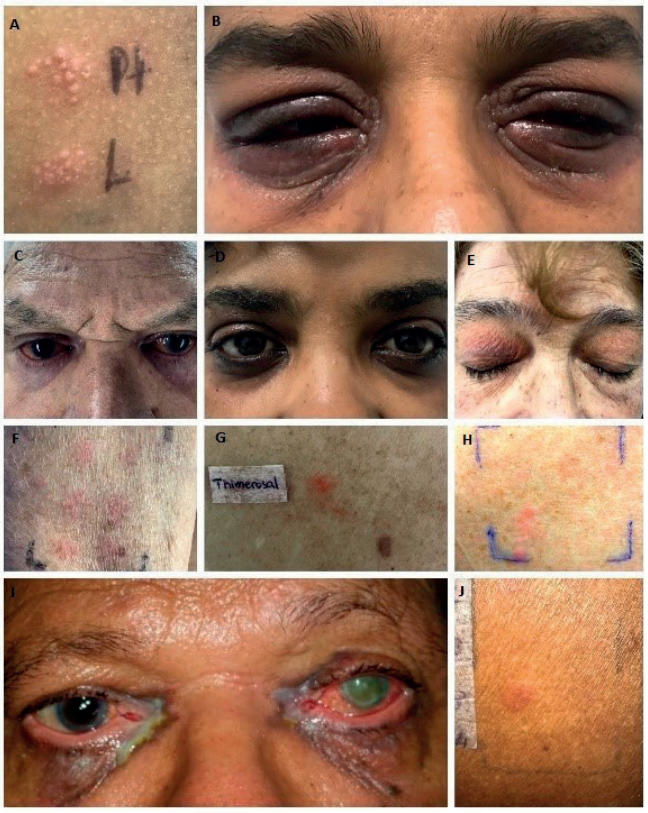
The patch test is used to detect and define possible exogenous chemical agents that can cause allergic contact dermatitis. These chemical agents can cause dermatitis by an immunologic (hypersensitivity) or non-immunologic mechanism (toxic).

The patch tests were carried out with the Standard Battery of the Brazilian Study Group of Contact Dermatitis, added with the Cosmetic Battery (4) and with the personal and continuous eye drops in use of each patient. The eye drops were tested as is, without dilution, directly in the filter paper and fixed to a Finn chamber. Two readings were performed on the tests that were applied, the first after 48 hours (D2) and the second after 96 hours (D4). The test is considered positive if erythema, edema, infiltration, and vesicles arise at the site of application of the substance and can be classified into degrees (+; + +; +++) depending on the intensity of the local reaction, as recommended by the International Contact Dermatitis Research Group (ICDRG) (4).

Table I *- Description of demographic data, ophthalmic disease, medications in use, results of late reading contact tests (96 hours reading) and clinical outcome of the 6 patients in our series.*

Patient and time of clinical complains	Eye disease (ophthalmological)	Eye drops in use	Positive substances in the late reading (D4) patch test	Clinical evolution after withdrawal of the involved substances
Patient 1. 79 yo White man 1 year	Glaucoma	Eye lubrificant Timolol Maleate 0.5% Dorzolamide 2% + Timolol 0.5% Bimatoprost Brimonidine tartrate	Timolol (+)	Full resolution of active lesions
Patient 2. 39 yo Black woman 2 months	Allergic conjunctivitis	Olopatadine hydrochloride 1.11% Alcaftadine 0.25% Sodium hyaluronate	Olopatadine hydrochloride (++) Alcaftadine (++) Ethylenediamine (++)	Absence of active injuries
Patient 3. 49 yo Black woman 2 years	Glaucoma, Keratoconus	Timolol Maleate 0.5% Travoprost 0.04 % Fluorescein Sodium	Nickel Thimerosal (++)	Improvement of eczema. Post-inflammatory dyschromia (hyperpigmentation)
Patient 4. 71 yo White woman 4 months	Glaucoma, Cataract, Bacterial conjunctivitis	Tropicamide 10mg / mL Phenylephrine 10mg / mL Hydrochloride Moxifloxacin 5.45% Prednisolone acetate 10 mg /mL Tobramycin 3 mg / mL	Prednisolone acetate (+)	Total resolution of skin change
Patient 5. 76 yo White woman 7 months	Glaucoma	Eye lubrificant Brinzolamide 10 mg / mL Timolol Maleate 0.5%	Brinzolamide (+)	Total eczema regression
Patient 6. 74 yo Black man 3 months	Glaucoma and Cataract	Atropine 0.5% Timolol maleate 0.5%	Atropine (+) Timolol (+)	Improvement of eczema

Figure 1 *- Clinical presentations and patch tests results in D4.*



(**A**) Positive Patch test to Olapatadine (++) and Alcaftadine (++). (**B**) Patient 2 described in table I. (**C**) Patient 1 described in table I. (**D**) Patient 3 described in table I. (**E**) Patient 4 described in table I. (**F**) Positive Patch test to all eye drops with Timolol (+) by Patient 1. (**G**) Positive Patch test to Thimerosal (+), (**H**) Positive Patch test to Prednisolone acetate (+). (**I**) Patient 6 described in table I. (**J**) Positive Patch test to Atropine (+).

Discussion

This study focused on characterizing the subgroup of patients referred for periorbital dermatitis with a positive patch test to ophthalmic medications during a span of 2 years. The characteristics of our patient population is similar to that of patients with periorbital dermatitis overall. A predominance of females among patients with periorbital dermatitis is well known from the literature (5-7). The female predominance has been attributed to the more common use of cosmetics and other topical products on the face. In our study, the mean age was 64 years. Landeck *et al.*, observed that patients with periorbital dermatitis related to topical ophthalmic medications were significantly older than controls and the other periorbital subgroup in a cross-sectional study with 4779 patients (7). The predominance in eldery age it was observed too in a 16,065 patients study made in Belgium (8).
Ophthalmologic solutions are an important trigger for periorbital contact dermatitis, with numerous compounds involved in the hypersensitivity reactions of contact eczemas, such as antibiotics and preservatives, including: thimerosal, benzyl alcohol, benzalkonium hydrochloride, ethylenediamine and parabens. The thin epidermis of the periorbital skin renders eyelids particularly sensitive to the hapten penetration and subsequent ACD. Glaucoma and cataract are the world's most frequents causes of acquired loss of eyesight. With the aging of the population, these pathologies are becoming more prevalent. Different kinds of eyedrops are available to control intraocular pression (IOP) in glaucoma and to retard the evolution of cataract or to prepare both for surgery intervention. It is recommended that treatment starts with only one drug, but several types of drugs are sometimes applied in combination. In such cases, the risk of contact dermatitis is more likely to increase. In recent years, the cases reports of contact dermatitis induced by different eyedrops are increasing (9, 10). The cases described include a variety of clinical presentations and severity, such erythema, papules or vesicles, swelling of the periorbital region, eyelid eczema, blepharoconjunctivits, conjunctival ecchymosis and visual blurring. Pruritus is strongly suggestive of contact allergy. Other manifestations include lichenification and postinflammatory hyperpigmentation in prolonged cases. Chronic scratching may lead to secondary infection, loss of eyelashes, or change in the tearing function.
ACD triggered by ethylenediamine, timolol, prednisolone acetate, brinzolamide, and atropine was observed in our cases, all confirmed by patch test, in a late reading (D4 or 96 hours reading). The late reading is fundamental because a sensitization reaction may occur more than 72 hours after contact. Furthermore, positive results of readings done 48 hours after application of the tests can become negative within 72-96 hours, meaning there was only local irritation due to test occlusion.
Although ophthalmic medications may be responsible for up to 20% of ACD, it is difficult to diagnose. First, the test is performed on the back which is much thicker skin than that of the eyelids and chemicals might not penetrate as easily. It is recommended to test the actual ophthalmic medication in addition to the standard ophthalmic tray available for patch testing as many chemicals in ophthalmic compositions are not a part of the commonly available kits (11). In Brazil, we do not have ophthalmic specific tray and the standard series and the lack of standardization of tests with specific batteries in Brazil since the ophthalmic substances are not part of the most available test batteries.

Conclusions

The ACD by ophthalmic drugs is becoming more frequent, caused by the increase of eye diseases diagnosis and the continuous use of topical medications. The main challenges for diagnosis are the high frequency of patch tests with false-negative in standard series. ACD by components of ophthalmic solutions must be remembered as a differential diagnosis in eyelids eczema, and periorbital regions by all practitioners, dermatologists,

allergists, and ophthalmologists considering its frequency, and the late diagnosis can bring significant eye sequelae. Further studies are needed not only to assess the appropriate concentration and vehicles for testing new drugs but also to standardize the methodology for applying unconventional patch test.

Ethics

All patients signed an informed consent form.

Conflict of interests

The authors declare that they have no conflict of interests.

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Can placebo challenge test (inducing a "nocebo effect") be a suitable model to assess stress-induced bronchial obstruction? Suggestions from the multidisciplinary Working Groups "Stress-Asthma" and "AAIITO Regione Campania"

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Key words

Adverse drug reaction; anxiety; bronchial asthma; bronchial obstruction; cholinergic tone; depression; increased cholinergic tone; hypersensitivity; nocebo effect; placebo challenge.

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Doi
10.23822/EurAnnACI.1764-1489.192

To the Editor,

we read with interest the excellent article of Bizzi *et al.* (1) reporting that female sex, older age and low level of education combined with a depressive tendency seem to be potential risk factors for "nocebo effect" appearing during oral challenge test in patients with drug adverse reactions (ADR).

They demonstrated that 10% of the examined patients reported respiratory symptoms (dyspnea and perception of laryngeal obstruction) as a consequence of the "nocebo effect" and this percentage was quite similar to that found in our previous Italian multicenter study (2). However, since the aim of study was a psychological assessment of these patients, they did not provide comments concerning the association between nocebo effects and respiratory symptoms in patients with ADR.

In other words, are reported respiratory symptoms (in asthmatics with real or "presumed" ADR) the consequence of a real bronchial obstruction, a condition associated to stress or both? It has been also demonstrated that inducible laryngeal obstruction, which is an induced and inappropriate narrowing of the larynx leading to symptomatic upper airway obstruction, can coexist with asthma (3). In fact, in this study, 42% of patients had objective evidence of both conditions, and symptoms possibly attributable to laryngeal obstruction are common (as "nocebo effect") following placebo administration (3).

Based on these premises, we would like to discuss the possibility to use placebo administration as "drug provocation test" and inducing a "nocebo effect", as a potential model to study the role of stress in triggering (or aggravating) bronchial obstruction in asthmatics (with a real or "presumed" ADR).

We have previously shown that about 63% of asthmatic patients reported the usual appearance of at least one non-respiratory symptom (n-RS) before an asthma attack (4). Anxiety, and to a lesser extent depression, represented the most common n-RSs in our study, suggesting that both disorders may have a possible role in the development and triggering of an asthma attack. Several studies have shown that psychological stress may enhance bronchial hyperreactivity through different mechanisms such as mast cell activation, mediator release, inflammation, and impairment of respiratory tolerance (5-7).

Another modality of inducing an increase in airway resistance in asthmatics (but also in healthy individuals) is the use of visual unpleasant stimulations such as bloody or highly-arousal surgery films. Ritz and co-workers (8-10) reported a significant relationship between psycho-social stress and stimulation of the cholinergic system, resulting in an increased airway resistance. The authors demonstrated that unpleasant visual stimulations (*i.e.*, bloody films) can rapidly induce (after 1-2 minutes) a vagal-mediated response associated with an increase of airway resistance assessed by impedance plethysmography and end-tidal PCO_2 by capnometry. In addition, measures of airway inflammation (indirect, fraction of exhaled nitric oxide), reactivity (direct, methacholine challenge), and/or reversibility were also obtained. Therefore, these findings suggest focusing the attention on the potential role of the parasympathetic system as a trigger of bronchial obstruction at least in a group of asthmatics reporting the usual onset of cholinergic-related n-RSs (*i.e.*, stress and/or anxiety) before an asthma attack. We have hypothesized that, in some individuals, this condition of enhanced basal cholinergic tone might play a predominant role in determining airway obstruction, compared with other well-known factors such as allergens, air pollutants, infections, or exercise (a new "asthma phenotype"?) (11).

The vagal hyperactivity induced by anxiety and stress in asthmatics also represents the basis of important considerations by a therapeutic point of view, such as the use of anticholinergic agents (12, 13).

Suggestions from "Asthma-Stress" and "AAIITO Regione Campania" Working Groups

Since organizing bloody films vision could be of difficult feasibility in outpatient settings, the use of placebo administration has the advantage of exploiting the patient's inherent fear of taking drugs and the ambient situation that simulates taking an "active" drug thus inducing a stress status. A subject suffering from asthma and anxiety/depression with a real or "presumed" history of drug-related adverse reaction represents the ideal candidate. Indeed, it is not relevant to have a proven drug allergy, but it is essential that the patient is convinced to be "allergic" to drugs.

The suggested flow-chart to evaluate the possible role of "nocebo effect" in the induction of bronchial obstruction in these asthmatics has been summarized in **figure 1**.

The occurrence of airways obstruction or the worsening of an already present obstruction as assessed by spirometric evaluation, indicates a likely relationship between the parallel onset of stress and bronchospasm. In case of development of an associated onset of other parasympathetic stress-related symptoms (*e.g.*, abdominal pain, reflux, dry mouth etc.), this could support our hypothesis of a possible "asthma phenotype" characterized by a high systemic cholinergic tone.

According to our previous study (11), a simple question exploring the presence of vagal-related n-RSs during the collection of anamnestic data could help identify asthmatics with an imbalance between sympathetic and parasympathetic systems. These individuals could benefit of a further diagnostic evaluation *e.g.*, oxygen and methacholine inhalation, neck suction, slow deep breathing assessed by multiple frequency Forced Oscillation Technique (FOT), measurement of resting heart rate and pupillometry of a possible higher basal cholinergic tone (14), Laryngeal Dysfunction Questionnaire (LDQ) (15) which might be elevated by a "nocebo effect" induced-psychological distress. Following this hypothesis,

our suggested procedure (**figure 1**) could be a useful method to assess if an induced stress is able to start or increase airway obstruction in the single asthmatic patient. This demonstration could have important diagnostic (*e.g.*, for asthma phenotyping), preventive (*e.g.*, for avoidance of stressing situations) and therapeutic consequences such as the importance of psychological support in these individuals. In addition, since the degree of cholinergic tone is likely to be different among asthmatics, we believe it is not possible to rule out that the effectiveness of anticholinergic agents such as tiotropium could be greater in patients with an increased degree of cholinergic tone (11-13). This potential increased responsiveness to tiotropium may be usefully exploited also in the event of poor treatment efficacy or occurrence of adverse events with the use of long-acting β_2-adrenoceptor agonists (LABAs) (16).

In conclusion, the currently available literature indicates that anxiety and related psychological disorders should be considered as mechanisms that might trigger airway inflammation, the onset of asthma attacks, and the severity of respiratory symptoms. We believe that our suggested diagnostic procedure could be a useful model to assess the relationship between an induced stress/anxiety condition and the onset or aggravating bronchial obstruction in asthmatics (with a real or "presumed" ADR). Further studies should be planned to confirm our hypothesis in clinical practice.

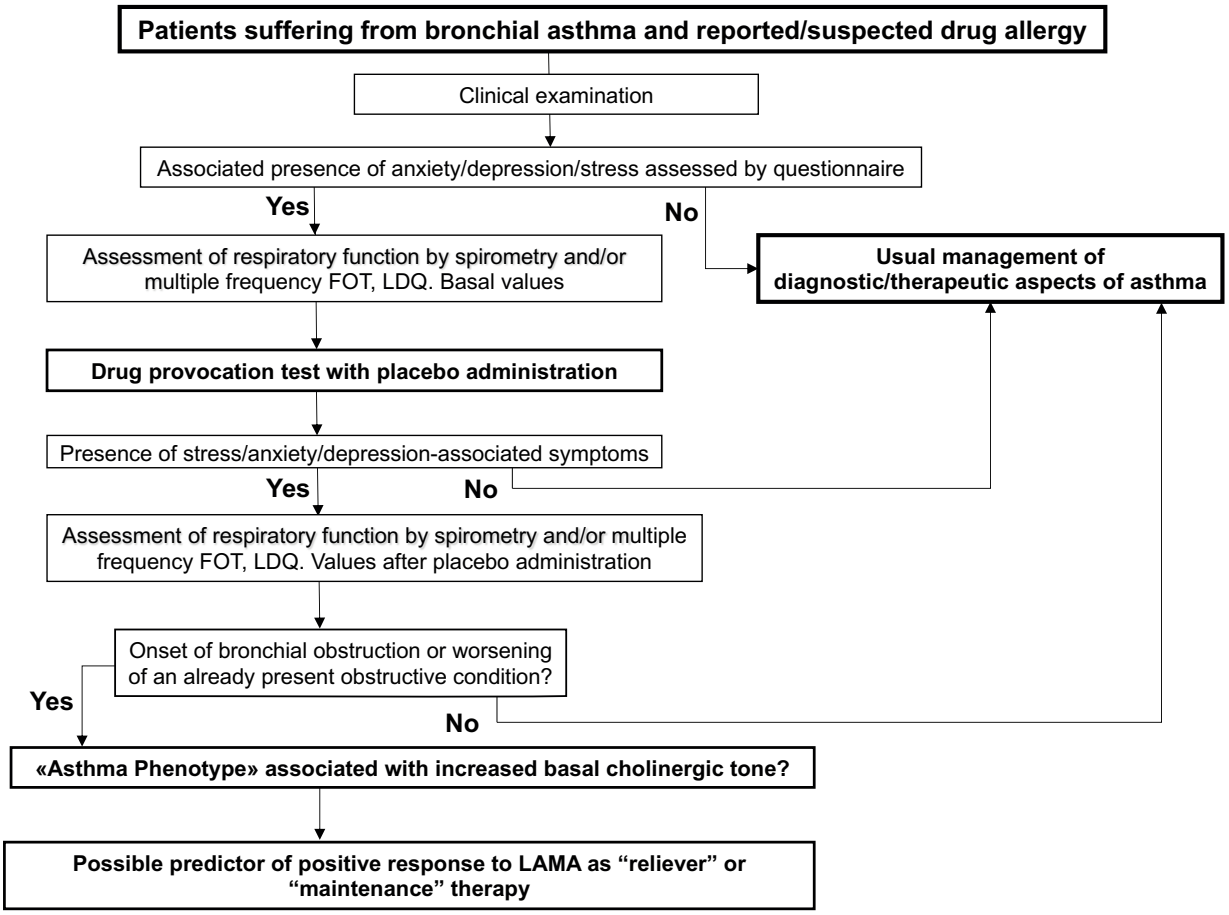
Acknowledgements

We thank the biologist Dr. Paola Berra and miss Lucia Franzese for technical assistance in the preparation of this manuscript.

Conflict of interests

The authors declare that they have no conflict of interests.

Figure 1 *- Suggested flow-chart to evaluate the possible role of "nocebo effect" in the induction of bronchial obstruction in asthmatics suffering from anxiety/depression.*



FOT: forced oscillation technique; LAMA: long-acting muscarinic antagonist; LDQ: laryngeal dysfunction questionnaire.

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Allergen immunotherapy in children with otitis media with effusion: a preliminary experience

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Key words

Otitis media with effusion; allergic rhinitis; childhood; allergen immunotherapy; house dust mites.

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Doi
10.23822/EurAnnACI.1764-1489.181

To the Editor,

Otitis media with effusion (OME) is characterized by the fluid present in the middle ear, behind an intact tympanic membrane, and without signs and symptoms of an acute infection (1). OME is very common because it has been reported that about 90% of children suffer from OME before school age (2). Physiologically, the middle ear is aerated 3-4 times /min from the Eustachian tube (ET) during swallowing. If ET function is compromised, a relative negative pressure develops in the middle ear, promoting fluid accumulation (3). In children, ET dysfunction mainly depends on post-infective or allergic inflammation and/or adenoid hypertrophy. Symptoms include hearing loss and feeling of ear fullness accentuated at night in the supine position. OME diagnosis is made through micro-otoscopy and tympanometry (1).
The efficacy of pharmacologic treatment is controversial (1). In persistent OME, myringotomy with tympanic paracentesis and trans-tympanic drainage positioning is an option. As a result, a careful workup is necessary to correctly manage OME, including the video-fiber-otoscopy of the nasal cavities and nasopharynx, analysis of oral functions allergy testing. The fundamental pathogenic role of allergy in OME is still debated in the literature (4, 5). There is mechanistic evidence that supports the role of allergic inflammation in ET dysfunction and fluid accumulation (6, 7). On the other hand, a direct demonstration of a causal mechanism exerted by allergy is still lacking. However, the prevalence of allergic disorders in OME patients may also be impressive, such as up to 80-90% (8, 9). In this regard, only one study has investigated the use of allergen immunotherapy (AIT) in OME patients (10). AIT lasted 2-8 years and was administered to 21 patients who refused the standard therapy. This study evidenced that AIT provided a completed resolution of effusion or drainage in 85% of cases. This study's relevance depended on the demonstration that AIT was able to improve OME acting on immune mechanisms. This outcome rekindled the interest in the role of allergic mechanisms in OME.
In this background, the current experience aimed to investigate whether AIT could improve OME in children with associated allergic rhinitis. In this open study, 20 children (mean age 9.4 years, range 6-12, 12 males) with OME and persistent allergic rhinitis (AR) due to *Dermatophagoides* were treated with a 2-year course of AIT for mites (Staloral 300, Stallergenes, Milan, Italy). Another

group of 20 children (mean age 8.9 years, range 6-12, 11 males) with OME and persistent AR was treated only with medications. The inclusion criteria were: age between 6 and 12 years, tympanometry type "B" in both ears, severe persistent AR, monosensitization to mites. Exclusion criteria were: recurrent respiratory infections, adenoid hypertrophy (grade 3-4), non-allergic rhinitis, mechanical obstruction of ET, septal deviation, oral breathing.
The Review Board approved the procedure of Azienda Sanitaria Provinciale of Catania. The parents signed informed consent.
The AIT schedule was five drops/3-time-week per sublingual route. All children were also treated with medications (oral antihistamines and/or intranasal corticosteroids) on demand.
The primary outcome was the change of tympanometry findings. We scored tympanometry considering the type of curve: type A (normal) = 0; type C = 1; type C1 (pressure < 200 mm-H_2O) = 2; type B = 3.
Children were examined at baseline (T_0) and every 6 months (T_{1-4}). The statistical analysis was performed using a t-test for independent samples.

AIT-Group

All children, but one, completed the AIT course. Ten (53%) children had a complete OME resolution, such as type A tympanometry in both ears at T_4. There was a significant reduction at T_3 and T_4 ($p < 0.001$ and < 0.0001, respectively). The tympanometry score's mean value was 3 at baseline and 0.64 at the end of the AIT course. The tympanometry outcomes were confirmed by otoscopic assessment. AIT was well tolerated, and no clinically relevant adverse events occurred.

Control-Group

Three children had a complete resolution of OME. The mean tympanometry score was 3 at baseline and 1.89 at T_4. The score reduction was not significant.

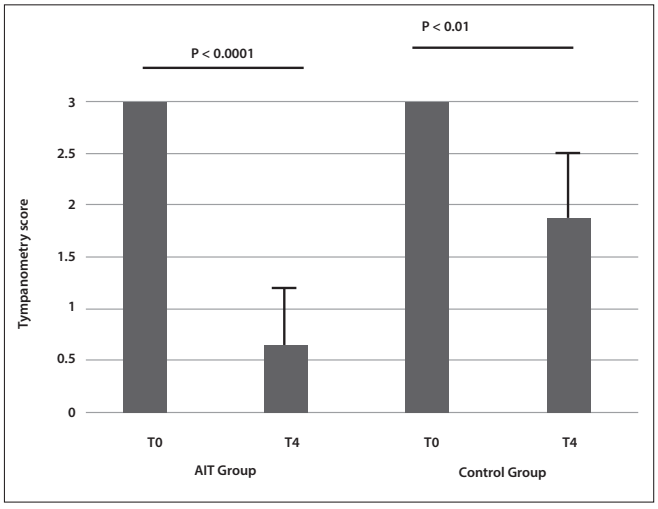
Intergroup analysis

The comparison between groups showed that AIT treatment was significantly more effective than medications alone ($p < 0.01$).
This open study demonstrated that OME completely disappeared in more than half of children after AIT. Tympanometry findings also significantly diminished as of 18 months (**figure 1**). AIT treatment was also more effective than pharmacological therapy.
The tympanometry improvement was consistent with the macroscopic observation of the eardrum. Notably, a relevant improvement was also observed in autumn-winter, such as when OME worsening is common. This fact could support the relevant pathogenic role of persistent AR. AR is characterized by type 2 inflammation (9). Type 2 inflammation is closely dependent on allergen exposure, so it is persistent in patients allergic to *Dermatophagoides* (12). Persistent allergic inflammation causes ET dysfunction and spreads in the middle ear promoting OME. Therefore, the current study provided a positive contribution to support a pathogenic role of allergy in OME development in patients with severe persistent AR.
The main limitations of this study were the open design, the lack of biomarkers assessment, the short AIT course, such as 24 months, the limited number of enrolled children considering the relatively high prevalence of OME, and the concomitant drug therapy, which could make difficult evaluate precisely the AIT effect. However, in clinical practice, only 10-20% of children with clinically relevant OME, such as bilateral tympanometry type B, spontaneously recover. The majority of patients are treated with intranasal corticosteroids, but with slight and transient results. Some OME children with associated adenoid hypertrophy tend to improve in summer and seaside staying, but allergic children do not. For this reason, children with OME and associated severe AR could fruitfully be treated with AIT. Therefore, the current study should be considered a preliminary experience, which should be confirmed by further controlled and randomized trials.
In conclusion, the present preliminary study is the second report showing that AIT could be useful in treating OME associated with severe persistent AR. Moreover, OME is an inflammatory disease, never infectious, frequently depending on persistent allergic inflammation. Thus, adequate treatment of allergy could significantly affect OME.

Conflict of interests

The authors declare that they have no conflict of interests.

Figure 1 *- Tympanometry score assessed at T_0 (baseline) and T_4 (after 24 months) in AIT-Group and Control-group.*



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