



## Original article

## Monosensitization and polysensitization in allergic rhinitis

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## ABSTRACT

**Background:** Polysensitization is common in patients with allergic rhinitis (AR) and may affect clinical feature. However, there are patients who remain monosensitized.**Objective:** This cross-sectional study aimed at evaluating a large cohort of AR patients to define the percentage and the features of mono- and poly-sensitized subjects.**Methods:** This observational cross-sectional study included a large group of AR patients: 2415 subjects (1958 males, mean age  $24.6 \pm 5$  years) were consecutively evaluated. Symptom severity, type and number of sensitizations, and AR duration were considered.**Results:** 621 patients (25.7%) were monosensitized: 377 to *Parietaria*, 194 to house dust mites, 19 to birch, 17 to grasses, 12 to molds, 2 to olive, and 1 to cypress. There was no difference between mono- and polysensitized patients concerning the duration of rhinitis ( $6 \pm 2.14$  years vs  $6 \pm 3.7$ ).Severity of symptoms was higher in polysensitized patients than in monosensitized ( $p < 0.05$ ); in addition, there was a difference among monosensitized patients: *Parietaria*-allergy induces the most severe symptoms.**Conclusion:** This study conducted in a large AR population might suggest that monosensitized and polysensitized AR patients could constitute two different categories. In addition, the specific type of allergy may condition the clinical feature.

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## 1. Introduction

Allergic rhinitis (AR) is the most frequent IgE-mediated disease, as its prevalence may be up to 40% of the general population [1], and causes substantial social and economic costs [2]. In fact, school or work performance and absences (including parents' work absences), daily activities and plays, and quality of sleep are significantly affected in both children and adults with AR [3]. AR may be also frequently associated with asthma as underlined by the ARIA (Allergic Rhinitis and its Impact on Asthma) document [4].

Moreover, the increasing number of sensitizations in the same allergic patient seems to characterize the natural history and may represent a common feature of allergic patients [5]. However, it has been documented that atopic infants start always with monosensitization [6].

Polysensitization is an immunological phenomenon that is clinically significant and relevant from an epidemiological point of view. Indeed, polysensitization has been well documented in several studies conducted both in children and in adults, during general population survey or in allergic population-based studies [7–13]. In addition, polysensitization concurs to the burden of AR as it may be associated with a more impaired quality of life than monosensitization [14].

On the other hand, there are patients who remain monosensitized over the years.

Moreover, AR is typically sustained by allergic inflammation which depends on allergen exposure. However, it has been reported that the inflammatory and clinical pattern is different on the basis of the specificity of the causal allergen [15]. Therefore, each allergen may induce a particular biological and clinical feature [15].

An unanswered question is whether monosensitized AR patients may present different clinical features in respect to polysensitized patients. Therefore, this cross-sectional study aimed to evaluate a large cohort of AR patients to define the percentage and the characteristics of monosensitized AR subjects.

## 2. Materials and methods

## 2.1. Study design and setting

This observational cross-sectional study included a large group of patients with allergic rhinitis. All of them were Navy soldiers who referred to Navy Medical Service for periodic fitness visit, in order to be allowed to attend specific courses (e.g., for pilot, frogman, diver, submariner, etc.). The visits were performed during the spring immediately before the beginning of class.

The Navy Review Board approved the study procedures and written informed consent was obtained from each subject.

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## 2.2. Subjects

Two thousand four hundred fifteen patients (1958 males, mean age  $24.6 \pm 5$  years) were consecutively evaluated. A detailed clinical history was taken and a complete physical examination was performed. The patients were included in the study on the basis of a clinical history of allergic rhinitis and AR diagnosis made according to validated criteria [4]. Exclusion criteria were: any prior history of asthma, chronic or acute upper respiratory infections, previous or current specific immunotherapy. All patients were treated with drugs (e.g. with antihistamines) only if actually needed. It should be noted that all subjects included in this study had no symptoms of lower airway disease or asthma. In fact, the military service does not accept subjects who have asthma or other known lung diseases.

## 2.3. Symptoms

The following nasal symptoms were assessed through questions made by the investigator: nasal obstruction, sneezing, rhinorrhea, and itchy nose. Each symptom was evaluated on the following scale: 0 = absent, 1 = mild (symptom was present but was not annoying or troublesome), 2 = moderate (symptom was frequently troublesome but did not interfere with either normal daily activity or sleep), and 3 = severe (symptom was sufficiently troublesome to have interfered with normal daily activity or sleep). Total symptom score (the sum of single scores) was calculated as previously reported [16].

## 2.4. Skin-prick test

Atopy was assessed by the presence of sensitization to the most common classes of aeroallergens by performing a skin-prick test. It was performed as stated by the European Academy of Allergy and Clinical Immunology [17]. The allergen panel consisted of the following: house-dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cat, dog, grasses mix, Compositae mix, *Parietaria judaica*, birch, hazel trees, *Olea europea*, cypress, *Alternaria*, *Cladosporium*, and *Aspergilli* mix. The concentration of allergen extracts was 100 immune reactivity/mL (Stallergenes, Milan, Italy). A histamine solution in distilled water (10 mg/mL) was used as positive control and the glycerol-buffer diluent of the allergen preparations was used as negative control. Each patient was skin tested on the volar surface of the forearm using 1-mm prick lancets (Stallergenes). The skin reaction was recorded after 15 min by evaluating the skin response in comparison with the wheal given by the positive and the negative control. A wheal diameter of at least 3 mm was considered as a positive reaction.

## 2.5. Statistical analysis

Descriptive statistics were calculated and reported in terms of frequencies and percentages for qualitative variables. Analysis of the Total Symptoms Scores between mono- and polysensitized patients was performed by means of the Student's *T* test; Analysis of the Total Symptoms Scores in the group of monosensitized patients was performed by means of non-parametric Analysis of Variance (Friedman's test).

Stata 10.1 (StataCorp, College Station, TX) was used for computation. A two-sided value of  $p < 0.05$  was considered statistically significant.

## 3. Results

Globally, 2445 patients were visited: 1824 (74.3%) were polysensitized and 621 (25.7%) were monosensitized as shown in Fig. 1.

Analyzing the monosensitized patients, 377 (61%) patients were sensitized to *Parietaria*, 194 (31.2%) to house dust mites, 19 (3%) to



Fig. 1. Percentage of frequency of 621 monosensitized and 1824 polysensitized subjects in the cohort of 2415 patients with allergic rhinitis.

birch, 17 (2.7%) to grasses, 12 (2.1%) to molds (interestingly there was no patient monosensitized to cat or dog), 2 to olive, and 1 to cypress as reported in Fig. 2.

There was no difference in age ( $25.6$  vs  $24.2$  years) and duration of rhinitis ( $6 \pm 2.14$  years vs  $6 \pm 3.7$ ) between mono- and polysensitized patients.

Severity of symptoms was significantly higher in polysensitized patients ( $6.94 \pm 2.2$  with C.I. 0.57) than in monosensitized ( $6.06 \pm 2.14$  with C.I. 0.55) ( $p < 0.05$ ) as reported in Fig. 3.

In addition, there was a significant difference among monosensitized patients: *Parietaria* ( $6.73 \pm 2.05$  with C.I. 0.52), HDM ( $5.03 \pm 1.93$  with C.I. 0.48), grasses ( $5 \pm 0.93$  with C.I. 0.38), birch ( $4 \pm 1.46$  with C.I. 0.41), and molds ( $5.08 \pm 1.97$  with C.I. 0.49).

*Parietaria*-allergy induces the most severe symptoms vs HDM ( $p < 0.05$ ), grasses ( $p < 0.01$ ), birch ( $p < 0.05$ ), molds ( $p < 0.05$ ), olive and cypress as shown in Fig. 4.

## 4. Discussion

Polysensitization is an immunological phenomenon that is clinically significant and relevant from an epidemiological point of view, as recently reported in recent surveys [5–13]. The increasing number of sensitizations seems to characterize the natural history of allergic patient and may represent a typical evolution of allergy. The percentage of polysensitized patients may widely range from 20 to 90% of evaluated populations [18]. Polysensitization may be also associated with different clinical features in respect to monosensitized patients, and especially with a more impaired quality of life [14,18]. A previous study demonstrated that allergic children had higher frequency of sensitizations than parents, mainly in family with polysensitizations [19]. Another study reported that polysensitized patients had more severe symptoms than monosensitized ones [11]. Moreover, it has been observed that polysensitized patients with

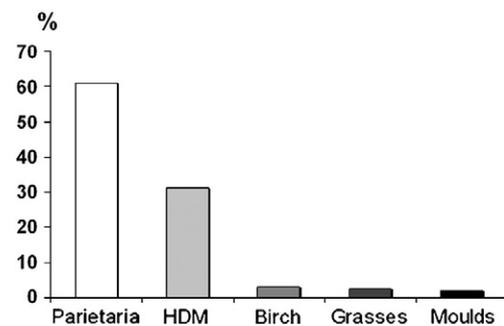


Fig. 2. Percentage of frequency of single sensitizations in the 621 monosensitized AR patients.

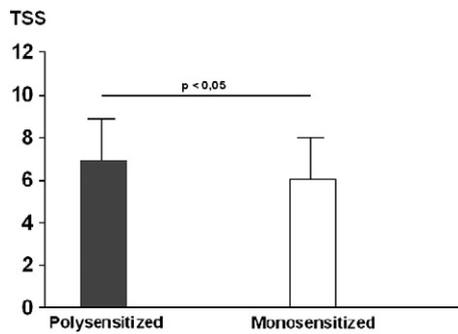


Fig. 3. Mean  $\pm$  S.D. of total symptom scores in 621 monosensitized and 1824 polysensitized AR patients (Student's *T* test).

rhinitis more frequently present associated asthma than monosensitized ones [18].

On the other hand, there are patients that remain monosensitized during their life. A very recent study supported an immunological hypothesis for explaining the trend to develop polysensitization: a functional defect of T regulatory cells [20]. Children with persistent monosensitization produced higher quantity of IL-10 and IFN- $\gamma$  than children developing polysensitization [20]. This fact might suggest the existence of two different phenotypes for mono- and poly-sensitized patients. Therefore, this study was designed for investigating the clinical characteristics of mono- and polysensitized patients in a large cohort of AR subjects.

Firstly, this study shows that polysensitization is very common as about 3/4 of patients were sensitized to more allergens. In addition, polysensitized patients had more intense symptoms than monosensitized ones. This finding is quite obvious as the allergic inflammation tend to be chronic in these patients so symptoms become persistent and severe. This issue has been well described in literature [16].

Secondly, there is no difference about the duration of rhinitis: this fact might mean that monosensitized patients may remain in this state over the time. It might support the possible existence of two distinct phenotypes for monosensitized and polysensitized subjects. In fact, it is well known that duration of allergic rhinitis may have profound impact in the natural history, mainly concerning the impairment of nasal function and the association with asthma [1,21]. Nevertheless, monosensitized had the same AR duration in comparison with polysensitized ones.

Thirdly, the type of allergy is relevant for characterizing clinical picture: *Parietaria* allergy causes the more severe symptoms. *Parietaria* is a pollen with a very long pollination period so that it may be con-

sidered an almost perennial allergen so the allergic inflammation is very persistent and may affect the clinical picture as previously reported [22].

Finally, there are allergens that rarely induce monosensitization and others that do not sustain monosensitization. This finding underlines a very relevant issue: the specificity of allergy. Recent studies has demonstrated that each allergen is able of causing a different immunological, inflammatory, functional, and clinical pattern, probably depending on own biological property [23,24]. In this regard the concept of periodicity of pollen allergy has to be abolished as evidenced by recent reports [25,26].

On the other hand, polysensitization may have a paramount relevance in clinical practice: for example, many physicians have doubts in choosing the allergen extract for allergen specific immunotherapy. In this regard, the evaluation of immunotherapy efficacy in polysensitized patients still represents an unanswered question and there are very few studies on this issue. Adkinson et al. conducted a controlled trial of subcutaneous immunotherapy (SCIT) in children with allergic asthma using several (up to 7) allergens and found no discernible benefit [27]. By contrast, Alvarez-Cuesta et al. demonstrated in a placebo controlled study that SCIT with both grass and olive pollens was able to significantly improve the quality of life in patients with seasonal allergic rhinitis due to double sensitisation [28]. A recent open study used sublingual immunotherapy (SLIT) to evaluate the respective efficacy of treatment with grass pollen, birch pollen, or both, in patients with double sensitization to such pollens [29]. SLIT with only grass pollen achieved some improvement in the season of birch pollen, and vice versa; the authors attributed this outcome to possible cross-reactivity of the two pollen allergens or to induction by the first SLIT treatment of production of interleukin 10, which exerts a partially nonspecific immunologic regulatory effect. However, SLIT with both pollens provided the best clinical outcome. Finally, a very recent study, based on real life clinical practice, provided an interesting observation: although the mean number of sensitizations was 3.65 in studied population, a single extract was chosen in about two thirds of patients, and few allergens were used in the remaining [30]. This study indicates that polysensitization should not constitute an impediment to SLIT prescription if only few allergens are chosen. Moreover, this choice seemed to be correct as SLIT efficacy was confirmed in that cohort also limiting the number of used allergens; in particular, the suitability of the allergen choice was confirmed by SLIT effectiveness on the reported improvement of AR and asthma classifications [30].

Polysensitization may have another clinical implication in patients with oral allergic syndrome that is frequently associated with pollen allergy, mainly concerning birch allergy. In this regard, the recombinant allergen-based concept of component-resolved diagnostic (CRD) and immunotherapy might be very relevant in the next future [31,32]. Overall, the evaluation of the so called "pan-allergens" might have a crucial role in managing polysensitized patients [33]. In fact, there are some "common" allergens, such as profilin and Ca binding proteins, which may cause skin prick positivities without real clinical allergy [34].

On the other hand, monosensitization seems to be characterized by a less severe clinical feature. However, the specific causal allergen may characterize the clinical profile.

*Parietaria* is characterized by a very protracted flowering period so the symptoms may be almost perennial if the climate is mild such as in Mediterranean area [35]. *Parietaria* is a relevant cause of respiratory allergy in many countries [35].

Grasses are the most common cause of hay fever in Europe: indeed it can be estimated that more than 40% of allergic patients are sensitized against grasses [36]. Pollen from different grass species, corn and other monocotyledonous plants contain a variety of different allergen molecules with cross-reactive potential. There are 6 groups of grass pollen allergens even though the grass pollen extracts used for

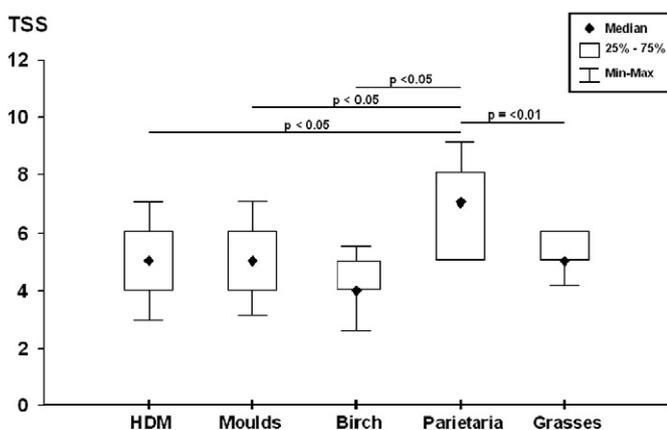


Fig. 4. Median, interquartile ranges, minimum and maximum of total symptom scores in Monosensitized AR patients considering each single causal allergen (Analysis of Variance: Friedman's test).

immunotherapy are mainly standardized regarding their contents of groups 1, 2, and 5 allergens, thus caution should be regarded in these patients. CRD may be useful in this situation: immunotherapy is not indicated if patients are negative for any of the four marker allergens of these groups (i.e. rPhl p1, p2, p5, p6) [37].

Olive allergen is characterized by a relatively short period of pollination, however it has been reported that symptoms may persist for long time after olive pollen season [38].

Birch allergy is very common in Scandinavia, however the major birch pollen allergen Bet v 1 (recognized by more than 95% of patients with birch allergy) cross-reacts with trees belonging to the order *Fagales* [39]. Moreover, Bet v 1 may trigger the synthesis of specific IgE antibodies that are capable of cross-reacting with its homologue in apple Mal d 1 (*Malus domestica*) [40].

Cypress pollen is present only during the winter and the symptoms due to cypressus allergy are particularly severe so that cypress allergy may be confounded with flu-like syndrome [41].

Finally, ragweed allergy is very common in North America and recently also in Europe [42], but there are no patients with ragweed monosensitization in our cohort.

On the other hand, perennial allergens, such as mites and pets, are important in younger patients because of the persistence of the exposure: indeed, allergen exposure causes inflammatory reaction, which is chronic in patients with perennial allergic rhinitis [43]. It is striking that there is no monosensitized patient to pets: this finding needs further re-evaluation.

This study conducted in a large cohort confirms that monosensitization is quite rare, whereas polysensitization is common as about 3/4 of patients are sensitized to more allergens. In this regard, it is to note that there are various publications from the Global Allergy and Asthma European Network (GA<sup>2</sup>LEN) which has been founded for responding to some unanswered questions. The first document standardized the procedure for skin prick test and defined a Paneuropean panel of allergen extract to be used for skin prick test [44], which is substantially similar to the panel used in the current study. Then, 18 European birth cohorts on asthma, allergic rhinitis and eczema were identified and assessed for future comparative studies [45]. Another publication established a standardized quality management system for the GA<sup>2</sup>LEN, so harmonized procedures can be achieved in an international health network and ensures quality of care [46]. However, the main aim of GA<sup>2</sup>LEN is to combat fragmentation in the European research area and to tackle allergy in its globality [47]. In this regard, the present study could give an adjunctive contribution concerning the relevant issue of polysensitization. Nevertheless, it is to note that a possible limitation of this study is represented by the methodology of study. In fact, patients were assessed only by skin prick test (for obvious economic reason). Unfortunately, skin prick test were performed only to subjects with symptoms, so there is no information about subjects with mono- or poly-sensitizations without clinical manifestations. This issue is clinically relevant as the assessment of differences between the asymptomatic and symptomatic groups of subjects represent one of the scientific programs of Global Allergy and Asthma European Network funded by the European Union [48].

It is important to underline that only the component-resolved diagnosis allows to reach more conclusive findings [49]: indeed, some skin positivities could not correspond to real clinical allergy, but to a cross-reactivity to “pan-allergens”.

Finally, it is to note that this study has some relevant limitations: i) the studied population was particularly selected as the patients were young adults and mostly males, ii) only allergic rhinitis was investigated, iii) only nasal symptoms were assessed, and iv) the different symptom severity between mono- and polysensitized patients might be not clinically relevant.

In conclusion, this study conducted in a large AR population might suggest that monosensitized and polysensitized AR patients could

constitute two different categories and also the specific type of allergy may be able of conditioning the clinical feature. However, further studies should be conducted in more heterogeneous populations to confirm these findings.

## Learning points

- Monosensitized and polysensitized AR patients could constitute two different categories.
- The specific type of allergy is able of conditioning the clinical feature.

## Conflict of interest

The authors state that there is no conflict of interest.

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