

Short communication

Allergic patients have more numerous and prolonged respiratory infections than nonallergic subjects

Background: Allergic disorders are characterized by type 2 helper T cell (Th2)-polarization, thus physiological type 1 helper T cell (Th1)-dependent mechanisms involved in fighting respiratory infections (RI) may be defective. It has previously been reported that allergic children have more numerous and severe RI than nonallergic ones.

Objective: The aim of the study was to evaluate the number and duration of RI in adult allergic and nonallergic subjects.

Methods: Six hundred and twenty-four subjects were studied; 202 of them were allergic (i.e. suffering from allergic rhinitis). The number of RI as well as the duration of the disease were recorded for 2 years.

Results: Allergic subjects showed a significantly higher rate of RI episodes [adjusted incidence rate ratio (IRR) = 2.16, 95% confidence interval (CI) 1.94–2.41, $P < 0.001$] than subjects without allergy. The number of mild RI episodes was slightly higher in allergic subjects (IRR = 1.68, 95% CI 1.50–1.89, $P < 0.001$), while the number of severe episodes was markedly higher (IRR = 15.71, 95% CI 10.35–23.84, $P < 0.001$) when compared with non-allergic subjects. Moreover, allergic patients showed a longer total duration of RI than nonallergic subjects, with a mean difference of 17.4 days (95% CI 15.5–19.4, $P < 0.001$).

Conclusions: This study provides evidence that adult allergic patients have more numerous and prolonged RI than nonallergic subjects.

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Allergic disorders show an increasing worldwide prevalence (1). The immunopathology of allergic rhinitis and asthma shares common mechanisms characterized by type 2 helper T cell (Th2)-dependent inflammation (2). As a consequence of it, the atopic subject develops a typical Th2-polarization with a type 1 helper T cell (Th1)-response reduction (2). Interferon-gamma, typical Th1-derived cytokine, is deputized in fighting infections. Thus, it has been pointed out that allergic patients could present higher susceptibility to contract respiratory infections (RI) rather than nonallergic subjects (3). This hypothesis could be reinforced by the evidence that rhinovirus infections are very common (4). Indeed, there is a clear link among allergen exposure, intercellular adhesion molecule 1 (ICAM1) expression, allergic inflammation and RI. The main receptor for rhinovirus is the adhesion molecule ICAM1 (4), and ICAM1 expression on nasal epithelial cells is strictly related to allergen exposure in allergic subjects (3). In addition, treatment with drugs able to reduce ICAM1 expression has shown to be able to lower both the number and the severity of RI in allergic children (5).

Respiratory infections are frequent in general population and constitute a demanding challenge for physicians (6).

Very recently, it has been evidenced that allergic children have more numerous and severe respiratory infections than nonallergic children (7).

Therefore, this study was performed to evaluate the number and duration of RI in adult allergic and nonallergic subjects to confirm previous findings observed in children.

Methods

Study design

This is a longitudinal prospective observational study conducted over a 2-year period in a large and healthy population of Navy soldiers. The study was approved by the Review Board and an informed consent was obtained from each participant.

The crew of some operative warships of the Italian Navy was enrolled in the study, with a total amount of 624 persons [472 males (75%) and 152 females]. Their mean age was 22.7 years (SD = 2.5). It is to note that Navy personnel is continuously checked and trained. All subjects were routinely visited each month, besides any visit related to sickness symptoms they might have been presenting. All the visits at the infirmary were recorded. Subjects were subdivided in two groups according to the presence of allergy (i.e. allergic rhinitis). Allergic rhinitis was diagnosed on the basis of positive history of nasal-ocular symptoms and skin-prick test (8). All the

allergic patients assumed oral antihistamines on demand only. Moreover, a diagnosis of asthma and of other allergies is incompatible with the military service.

Among subjects with allergy, 29 (14%) were monosensitized and 173 (86%) polysensitized. A median number of three sensitivities [interquartile range (IQR) 2–4] was recorded over the eight tested allergens (house dust mites, grasses, *Parietaria*, olive tree, birch, hazel, cat and dog).

The diagnosis of RI was made when at least two symptoms or fever and one symptom (axillary temperature $\geq 38^{\circ}\text{C}$) were present for at least 48 h. The symptoms taken into consideration for diagnostic purposes were: mucopurulent rhinorrhea (stuffy and/or dripping nose), sore throat, cough (dry or productive), otalgia (earache), fever, dyspnoea and mucopurulent secretion.

The primary end-point was to compare the number of RI episodes recorded during the study period in the two groups of allergic and nonallergic subjects; the role of polysensitization was also assessed. The secondary outcome was to compare the total duration of RI episodes in days, as well as the number of severe and mild RI episodes between the two groups. Respiratory infections were considered as mild or severe according to validated published criteria (9). Mild RI involved the rhinopharynx (rhinitis, rhinopharyngitis with possible involvement of tonsils) and/or the larynx. Severe RI involved the middle ear, the paranasal sinuses or the lower airways.

Statistical analysis

We have described continuous data as mean and SD or median and IQR, and categorical data as counts and percentages. We computed the mean count (or mean rate) of RI episodes over the 2-year follow-up, and its exact 95% Poisson confidence interval (95% CI). We have compared age and gender between allergic and nonallergic patients by means of the Student's *t*-test and the Fisher's exact test, respectively. We assessed the role of allergy and of polysensitization on the rate of RI by fitting a Poisson model. Goodness of fit was verified with a test on deviances. We reported the incidence rate ratio (IRR) and its 95% CI as a measure of effect. Being the one considered an otherwise healthy population, estimates were only adjusted for age and gender. We have eventually compared the total duration of RI episodes by means of the Mann–Whitney U test or the Kruskal–Wallis test. The mean difference between groups and its 95% CI was also computed.

Stata 9.2 (StataCorp, USA) was used for computation. A two-sided *P*-value < 0.05 was considered statistically significant. For *post-hoc* comparisons, the significance was set to 0.017, according to the Bonferroni correction.

Results

Population

Six hundred and twenty-four subjects were globally enrolled in the study. Allergic rhinitis was diagnosed in 202 subjects (152 males, 50 females; mean age 23.7 ± 2.0 years), whereas 422 subjects were nonallergic (319 males and 103 females, $P = 0.921$; mean age 22.2 ± 2.7 years, $P < 0.001$). Allergic subjects were sensitized to: house dust mites (80%), grasses (66%), *Parietaria* (43%), olive tree (27%), birch (23%), hazel (19%), cat (14%) and dog (6%). On the whole, we have observed a low rate of RI over the 2 years of observation, with mean rates per soldier of 2.2 total episodes (95% CI

2.1–2.3), of 0.34 severe episodes (95% CI 0.30–0.39) and of 1.9 mild episodes (95% CI 1.8–2.0).

Primary outcome

Allergic subjects showed a significantly higher rate of RI episodes (adjusted IRR = 2.16, 95% CI 1.94–2.41, $P < 0.001$) than subjects without allergy, as detailed in Table 1. However, no difference was observed between subjects with poly- vs monosensitization (adjusted IRR = 1.05, 95% CI 0.85–1.31, $P = 0.618$).

Secondary outcomes

The number of mild RI episodes was slightly higher in allergic subjects (IRR = 1.68, 95% CI 1.50–1.89, $P < 0.001$), while the number of severe episodes was markedly higher (IRR = 15.71, 95% CI 10.35–23.84, $P < 0.001$) with respect to nonallergic subjects (Table 1). Mono- and polysensitized subjects did not have different rates neither of severe RI (IRR = 1.20, 95% CI 0.78–1.86, $P = 0.407$) nor of mild RI (IRR = 1.02, 95% CI 0.79–1.30, $P = 0.892$).

Moreover, allergic patients showed a longer total duration of RI than nonallergic subjects, with a mean difference of 17.4 days (95% CI 15.5–19.4, $P < 0.001$); poly- and monosensitized subjects did not elicit significant differences in duration (4.2 days, 95% CI -1.3–9.5, $P = 0.115$). Similarly allergic subjects had a longer total duration of severe RI than nonallergic subjects, with a mean difference of 11.6 days (95% CI 10.1–13.1, $P < 0.001$), and of mild RI, with a mean difference of 5.8 days (5.0–6.7, $P < 0.001$) (Table 1). Mono- and polysensitized subjects did not show a difference in duration neither for severe RI (mean difference 3.7 days, 95% CI -0.8–7.5, $P = 0.055$) nor for mild RI (mean difference 0.5 days, 95% CI -2.0–3.1, $P = 0.682$).

Discussion

Not unexpectedly, this study showed that RI is a rare event in this population of otherwise healthy Navy soldiers, with a mean rate of two episodes per soldier over the 2-year follow-up, and that severe RI is even less frequent (with a mean rate of one episode for every three soldiers over 2 years). Our results have also underlined another important aspect of the disease, showing that allergic subjects have more frequent and prolonged RI than nonallergic ones. We have observed a two-fold increase of RI risk in allergic subjects, and a duration almost 3 weeks longer of the symptoms than in nonallergic. This phenomenon is particularly evident for severe RI, with a 15-fold risk increase in allergic patients. It has to be explicitly stated that no relevant difference exists between subjects presenting with mono- vs polysensitiza-

Table 1. Association of allergy with the primary and secondary endpoints over the 2-year follow-up

Endpoint	Allergy	Rate (95% CI)	IRR (95% CI)	<i>P</i> -value	Sensitization	Rate (95% CI)	IRR (95% CI)	<i>P</i> -value	
Primary endpoint									
Total RI count	No	1.6 (1.5–1.7)	1	< 0.001	None	1.6 (1.5–1.7)	1	< 0.001	
	Yes	3.5 (3.3–3.9)	2.16 (1.94–2.41) *		Mono	3.3 (2.7–4.1)	2.06 (1.66–2.56) *		
					Poly	3.5 (3.3–3.8)	2.18 (1.94–2.44) *		
Secondary endpoints									
Severe RI count	No	0.06 (0.04–0.09)	1	< 0.001	None	0.06 (0.04–0.09)	1	< 0.001	
	Yes	0.9 (0.8–1.1)	15.71 (10.35–23.84)		Mono	0.8 (0.5–1.2)	13.39 (7.60–23.58)		
					Poly	0.9 (0.8–1.1)	16.10 (10.57–24.52)		
Mild RI count	No	1.5 (1.4–1.7)	1	< 0.001	None	1.5 (1.4–1.7)	1	< 0.001	
	Yes	2.6 (2.4–2.8)	1.68 (1.50–1.89)		Mono	2.5 (2.0–3.2)	1.66 (1.30–2.11)		
					Poly	2.6 (2.4–2.8)	1.69 (1.50–1.90)		
Total RI duration (days)		Median (IQR)	Mean difference (95%CI)	<i>P</i> -value		Median (IQR)	Mean difference (95%CI)	<i>P</i> -value	
	No	7 (5–10)	17.4 (15.5–19.4)		< 0.001	None	7 (5–10)		
	Yes	23 (13–34)			Mono	17 (10–28)	13.8 (8.9–18.7)		
Severe RI duration (days)					Poly	24 (13–34)	18.0 (15.9–20.2)		
	No	0 (0–0)	11.6 (10.1–13.1)	< 0.001	None	0 (0–0)		< 0.001	
	Yes	12 (0–17)	Mono		8 (0–15)	8.4 (5.0–11.9)			
Poly			12 (0–18)		12.1 (10.5–13.8)				
Mild RI duration (days)	No	6 (5–9)	5.8 (5.0–6.7)	< 0.001	None	6 (5–9)		< 0.001	
	Yes	11 (8–17)	Mono		10 (8–15)	5.4 (3.0–7.8)			
			Poly		12 (8–17)	5.9 (5.0–6.9)			

*Estimates adjusted for age and gender in a multivariable analysis; all *post-hoc* comparisons of mono- and polysensitized vs nonallergic subjects are significant at the 0.017 level (Bonferroni correction); no comparison between mono- and polysensitized subject is significant at the 0.017 level.

Abbreviations as in text.

tion, neither for the rate of RI nor for their total duration. The duration of the study and the large sample size further support our conclusions.

A possible explanation for these findings is that allergic reaction is characterized by mucosal inflammation that predisposes to infection. In addition, allergic subjects express ICAM1, an adhesion molecule involved in inflammatory events as ligand of lymphocyte function-associated antigen-1, expressed on leukocytes. Intercellular adhesion molecule 1 is also the main receptor for rhinovirus (3). Moreover, allergic patients present a typical Th2-polarization with a consequent reduced Th1-response that is supposed to adequately fight infections mainly through Interferon gamma. Eventually, the impaired reparative events and recovery in allergic patients, may explain the prolonged duration of RI.

On the contrary, it should be considered that allergic patients may refer more often to the physician, may have nasal hyperreactivity, leading to prolonged and/or more obvious symptoms than normals, and at least some of the observed symptoms may not be colds but episodes of rhinitis that were misinterpreted by the patient/doctor. Moreover, we have to consider that an important drawback of this study is the absence of cultural, viral or bacterial, determination.

It is to underline that the relationship between allergy and RI is of considerable interest as there are few studies over this topic and findings are conflicting. In this regard, a study performed by Bardin demonstrated

that experimental rhinovirus cold in atopic subjects heightened susceptibility to the detrimental effects of colds both concerning immunological and clinical aspects (9). Another study of the same group reported that atopic asthmatics are not at greater risk of rhinovirus infection when compared to healthy individuals; still, they suffer from more frequent lower-respiratory-tract infections and have more severe and longer-lasting lower-respiratory-tract symptoms (8). Moreover, Xepapadaki has recently evidenced that in asthmatic children the duration of airway hyperreactivity, evaluated by methacholine bronchial challenge, after a single natural cold was from 5 to 11 weeks (10). However, this study highlighted that an increased rate of symptomatic cold and asthma episodes in atopic children was associated with considerable cumulative prolongation of airway hyperreactivity. This event might help to explain the role of atopy as a risk factor for asthma persistence (10). Anyway, most of these previous studies focussed on asthma, rather than rhinitis and do not differentiate between the atopic element and the respiratory element, such as asthma.

In conclusions, this study provides evidence that allergic patients have more numerous and prolonged RI than nonallergic subjects. Therefore, it confirms previous findings and demonstrates that atopics are more susceptible than nonallergic subjects to present with RI. Further studies should be addressed in order to investigate if anti-allergic treatments could improve this feature.

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