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The complex link between severity of asthma and rhinitis in mite allergic patients

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Summary
Aim: The aim of the study was to evaluate the link between the severity of upper and lower airways diseases in mite allergic patients with respiratory allergy.
Patients and method: A multicentre, observational, cross-sectional study was carried out in 556 consecutively enrolled mite allergic patients with rhinitis and asthma comorbidity attending a specialist unit. Severity assessment of rhinitis and asthma was evaluated in accordance with ARIA and GINA guidelines.
Results: Reliable data were available for 518 patients. The distribution of rhinitis severity was: 15.6% mild intermittent rhinitis, 4.4% moderate-severe intermittent rhinitis, 30.3% mild persistent rhinitis and 49.6% moderate persistent rhinitis. The distribution of asthma severity was: 41.3% mild intermittent asthma, 14.3% mild persistent asthma, 19.1% moderate persistent asthma and 25.3% severe persistent asthma. In patients with moderate-severe persistent rhinitis (49.5%) a significant trend ($p = 0.005$) was found pointing to an increased link with asthma severity.
Conclusion: A link between respective severities of rhinitis and asthma was found in only half of mite allergic patients with rhinitis and asthma.

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Introduction

The prevalence of rhinitis and asthma is increasing worldwide, this trend is also present in Italy where among the general population prevalence is greater than 25% for rhinitis and 5% for asthma.[1] Rhinitis and asthma frequently coexist: it is estimated that rhinitis affects 80% of the asthmatic population and that between 20 and 50% of patients with allergic rhinitis report asthma or asthma-like symptoms.[2,3]

The United Airways Diseases (UAD) hypothesis postulates that rhinitis and asthma are manifestations of a single inflammatory process, leading to disease of both the upper and lower airways. In brief, rhinitis is the initial clinical presentation of such inflammatory process, and as its severity grows, lower airways are clinically involved.[3–6] Therefore the severity of the disease is the central issue in this hypothesis, unfortunately severity measures, particularly for rhinitis, are inconsistent and dependent primarily on subjective reports about symptoms and treatment.

Even though evidence exists supporting the UAD hypothesis — in particular that rhinitis is associated with the onset of asthma, and that severity of rhinitis is associated with the prevalence and severity of coexisting asthma[6–10] — other data fail to show a link between severity of the two diseases.[11–14]

Further proof supporting the differences between rhinitis and asthma is provided by genetics.

It has become clear that there are separate genetic polymorphisms that affect susceptibility to allergic sensitization while totally different genes are associated with allergic diseases: genes identified in allergy are mostly involved with mechanisms regulating the balance of immune responses whereas disease-specific genes are mostly associated with the epithelial functions.[15]

The results of surveys concerning rhinitis and asthma comorbidity are highly dependent on the disease-defining criteria,[5] therefore a targeted study, with a homogenously selected group of patients with coexisting rhinitis and asthma could help shed some light on this issue.

Allergic sensitization to indoor allergens is the most influential risk factor for the onset of asthma[16,17] and the peculiar features of mite allergens enhance the development of asthma,[18] therefore the aim of this study was to evaluate the link between the severity of upper and lower airways diseases in symptomatic mite allergic patients attending a specialist medical setting for consultation.

Materials and methods

Study design

A multicentre, observational, cross-sectional study involving allergy and pulmonologist units throughout Italy was carried out. Participation was accepted via e-mail following invitations to collaborate sent to the 570 members of the AAITO association (Italian Association of Territorial and Hospital Allergists and Immunologists). Forty-three units joined the survey, nine subsequently dropped out for reasons unrelated to the study. The patients enrolled signed an informed consent form and completed the section for the patient of a two-part questionnaire. The patient section of the questionnaire collected the basic demographic details. The physician part of the questionnaire was designed to gather some relevant clinical information (clinical diagnosis of mite allergic rhinitis and asthma; duration of the disease; current therapy; self reported presence of coexisting sinusitis; nasal polyps and gastro-oesophageal reflux; rate of asthma exacerbations and related health care resource use) and to assess rhinitis and asthma severity, in accordance with the ARIA and GINA classifications.

The study was approved by the ethics committee.

Patients

All consecutively enrolled patients attending a specialist unit from September 1st 2007 to December 31st 2007, aged 14 and older, with a history of rhinitis and asthma, with symptoms in the last year and evidence of house dust mite allergy were eligible for the study.

As part of the inclusion criteria, a clinical diagnosis of rhinitis and asthma was certified by a pulmonologist and/or allergy specialist. Diagnosis of asthma was supported by: (1) affirmative answers to the following questions: "In the past 12 months, have you experienced wheezing or whistling in your chest?" or "In the past 12 months, have you taken any asthma medication?"; (2) a positive bronchodilation test (minimum 12% relative improvement in the volume FEV_1 after bronchodilator administration) and/or a prior positive methacoline test (PC20 $<$ 16 mg/ml) when available.

In accordance with ARIA guidelines,[19] severity of rhinitis was evaluated by combining the duration of symptoms with the disease's impact on patients quality of life and classified as follows: intermittent ($<$4 days/week or $<$4 weeks/year) and persistent ($>$4 days/week and $>$4 weeks/year). Rhinitis was diagnosed as moderate-severe in patients who replied "yes" to one or more of the following items: abnormal sleep; impairment of daily work or school; impairment of leisure activities; presence of troublesome symptoms. Rhinitis was classified as mild in patients who replied "no" to all of the above listed items.

Asthma severity, in accordance with the GINA 2006 classification algorithm, was ascertained using a grid sheet (Table 1), cross-checking the patient's level of symptoms and his/her level of treatment.[20]

Patients were classified as mite allergic, provided that at least the following two conditions were satisfied: a structured allergy history consistent with mite allergy (predominant symptoms, seasonality of symptoms and exacerbating factors) and a positive skin prick test.

Skin prick testing was performed in all patients with a panel of the most relevant inhalant allergens in Italy (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, *Alternaria*, *Cladosporium*, Grass mix, *Parietaria*, *Olea*, Cypress, Birch, Hazel, *Artemisia*, *Ambrosia*, Dog, Cat) (ALK-Abello A/S, Horshølm, Denmark and Stallergenes, Antony, France). A mean wheal diameter $\geq$3 mm was considered positive.

Table 1 Modified from: guidelines for the diagnosis and management of asthma. National Institutes of Health[20].

Clinic characteristics	Treatment steps			
	As needed short-acting β2-agonist			
	No therapy	Low-dose ICSs, leukotriene modifiers, theophylline, cromolyn, or nedocromil	Low-dose/medium-dose ICSs plus inhaled LABA or medium-dose ICSs; low-dose/medium-dose ICSs plus either leukotriene modifier or theophylline	High-dose ICSs and LABA plus systemic corticosteroids if needed (consider monoclonal anti-IgE)
Symptom less than once a week Brief exacerbation Nocturnal symptoms not more than twice a month FEV_1 or PEF $\geq$ 80% predicted PEF or FEV_1 variability <20%	Intermittent	Mild persistent	Moderate persistent	Severe persistent
Symptom more than once a week but less than once a day Exacerbations may affect activity and sleep Nocturnal symptoms more than twice a month FEV_1 or PEF $\geq$ 80% predicted PEF or FEV_1 variability <20—30%	Mild persistent	Moderate persistent	Severe persistent	Severe persistent
Symptom daily Exacerbations may affect activity and sleep Nocturnal symptoms more than once a week Daily use of inhaled short-acting β2-agonist FEV_1 or PEF 60—80% predicted PEF or FEV_1 variability <30%	Moderate persistent	Severe persistent	Severe persistent	Severe persistent
Symptom daily Frequent exacerbations Frequent nocturnal asthma symptoms Limitation of physical activities FEV_1 or PEF $\leq$ 60% predicted PEF or FEV_1 variability >30%	Severe persistent	Severe persistent	Severe persistent	Severe persistent

Patients with a cutaneous sensitization to other inhalant allergens were enrolled as well, but only if mite sensitization was judged by the doctor to be clinically relevant, in light of the structured allergy history, and when a clinical impact of other perennial allergens (i.e. cat or moulds) could be excluded.[21] During enrollment patients with symptoms and clinical allergy significant related to pollens were excluded, furthermore severity assessment was limited to late summer and autumn months when clinical confounding pollen allergy is minimal.

Statistics

Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS), version 13.0 for Windows. Descriptive statistics were presented as number and percentages for qualitative variables.

Bivariate analyses (chi-square test and analysis of variance) were carried out for estimating prevalence rates (categorical variables) and mean values (continuous variables). A linear-by-linear (Mantel—Haenszel test) association trend test was used to test the presence of a linear trend of proportions between the severity levels of rhinitis versus severity levels of asthma.

$p < 0.05$ was considered to be statistically significant.

Results

General characteristics of the sample population

Five hundred and ninety-eight patients were enrolled, 42 of which were excluded as they did not fit the selection criteria. Complete data concerning the assessment of the severity of coexisting rhinitis and asthma was available in

Table 2 Demographic characteristics and clinical data of study participants.

Sample size	Patients
Gender (514/518 pts)	
Male	40%
Female	60%
Age (years) (515/518 pts)	
Mean	35 years
Range	14–76 years
Median	34 years
Smoking status (518 pts)	
Never smoked	76.4%
Current	13.2%
Former	10.4%
Sensitization (518 pts)	
Mite mono-sensitized	31.0%
Mite plus other sensitizations	69.0%
Comorbidity (516/518 pts)[a]	
Sinusitis	13.2%
Nasal polyps	4.3%
GERD	10.9%
Current therapy (510/518 pts)	
Rhinitis	40.6%
Asthma	56.0%

GERD: gastro-oesophageal reflux disease.
[a] Comorbidities with prevalence greater than 4% are tabulated.

518 patients. The most important demographic and clinical features of the patients are presented in Table 2. The sample was made up of young adults who were quite evenly distributed throughout Italy. One third of the population had a single allergic sensitization to house dust mites. The majority of patients were receiving drug therapy for asthma and/or rhinitis. Concerning rhinitis severity, 81 (15.6%) patients had mild intermittent rhinitis, 23 (4.5%) patients had moderate-severe intermittent rhinitis, 157 (30.3%) patients had mild persistent rhinitis, and 257 (49.6%) patients had moderate persistent rhinitis. Concerning asthma severity, 214 (41.3%) patients had mild intermittent asthma, 74 (14.3%) patients had mild persistent asthma, 99 (19.1%) patients had moderate persistent asthma, and 131 (25.3%) patients had severe persistent asthma (Table 3). The association between some markers of asthma severity (i.e. patient-reported health care resource use, presence of comorbidities) independent from the GINA grading validated the assessment of asthma severity (Tables 4 and 5).

Interplay between the severity of rhinitis and asthma

Distribution of rhinitis and asthma severities, respectively, was reported (Fig. 1).

As a whole, no association was found between severity of rhinitis and severity of coexisting asthma (Table 3) ($\chi^2 \cdot p = 0.2$) however the evidence of a statistically significant test for trend (linear by linear $p = 0.015$), has suggested the presence of a possible correlation within the sample of patients.

This result was confirmed even after the exclusion of patients with a case history positive for sinusitis and/or nasal polyposis ($\chi^2 \cdot p = 0.61$ – linear by linear $p = 0.014$) (data not shown).

Indeed, a statistically significant trend of increase in prevalence within the moderate severe persistent rhinitis group by increasing asthma severity was documented ($\chi^2 \cdot p = 0.03$ – linear by linear $p = 0.005$).

Discussion

Our study provides evidence of a complex relationship between the respective severities of rhinitis and asthma; a clear link is in fact conclusively present in only half the surveyed population, precisely the group of patients with moderate-severe persistent rhinitis.

The patient selection and the severity of the diseases are probably involved in discordances between our results and those of two similar surveys.[8,9]

The first issue seems prevalent in the discordance with the result of the survey carried out in France.

In this questionnaire-based survey, among more than 14,000 patients, attending a general practitioner for asthma, an association between the prevalence and severity of allergic rhinitis and severity of asthma were found.[8]

Indeed, other surveys showed a stability or decrease of allergic rhinitis prevalence and an increase in prevalence of rhinosinusitis in patients with severe asthma compared with milder degrees of asthma severity.[9,22–24] The insufficient reliability of a questionnaire without skin prick tests or specific IgE measurements when assessing allergic rhinitis diagnosis was suggested.[21] Moreover the high sensitivity but poor specificity of questionnaires for rhinitis in distinguishing rhinitis from rhinosinusitis was documented.[22] These biases could be involved in the results of this study.

A study evaluating the impact of rhinitis on asthma control in patients with severe asthma, documented that

Table 3 Prevalence rates (%) of rhinitis severity levels in relation to asthma severity levels (p = n.s.).

	Intermittent asthma	Mild persistent asthma	Moderate persistent asthma	Severe persistent asthma	Total pts
Mild intermittent rhinitis, *n* (%)	38 (17.7)	13 (17.6)	11 (11.1)	19 (14.5)	**81 (15.6)**
Moderate-severe intermittent rhinitis, *n* (%)	13 (6.1)	4 (5.4)	2 (2.0)	4 (3.0)	**23 (4.5)**
Mild persistent rhinitis, *n* (%)	70 (32.7)	24 (32.4)	30 (30.3)	33 (25.2)	**157 (30.3)**
Moderate-severe persistent rhinitis, *n* (%)	93 (43.5)	33 (44.6)	56 (56.6)	75 (57.3)	**257 (49.6)**
Total pts	**214 (41.3)**	**74 (14.3)**	**99 (19.1)**	**131 (25.3)**	**518 (100)**

Table 4 Patient-reported health care resource use during the past year presence by asthma severity grade.

	Intermittent asthma *n* (%)	Mild persistent asthma *n* (%)	Moderate persistent asthma *n* (%)	Severe persistent asthma *n* (%)	*p*
GP visit (508/518 pts)					
• From 0 to 2 visits	185 (88.9)	48 (66.7)	72 (73.5)	69 (53.1)	<0.0001
• From 3 to 5 visits	23 (11.1)	24 (33.3)	26 (26.5)	61 (46.9)	
Specialist visit (506/518 pts)					
• From 0 to 2 visits	182 (87.9)	54 (76.1)	73 (74.5)	79 (60.8)	<0.0001
• From 3 to 5 visits	25 (12.1)	17 (23.9)	25 (25.5)	51 (39.2)	
Use systemic steroids (505/518 pts)					
• From 0 to 1	157 (77.0)	47 (65.3)	76 (77.6)	79 (60.3)	0.003
• From 2 to 5	47 (23.0)	25 (34.7)	22 (22.4)	52 (39.7)	
Visit emergency room (508/518 pts)					
• Yes	19 (9.1)	5 (6.9)	9 (9.3)	21 (16.0)	n.s.
• No	189 (90.9)	67(93.1)	88 (90.7)	110(84.0)	
Admission to hospital (506/518 pts)					
• Yes	1 (0.5)	2 (2.8)	3 (3.1)	4 (3.1)	n.s.
• No	206 (99.5)	70 (97.2)	94 (96.9)	126(96.9)	
Absence from job/school (503/518 pts)					
• Yes	33 (16.0)	20(28.2)	25 (25.8)	39 (30.2)	0.012
• No	173 (84.0)	51 (71.8)	72 (74.2)	90 (69.8)	
All 6 variables (518/518pts):					
• Yes	83 (38.8)	45 (60.8)	54 (54.5)	101 (77.1)	<0.0001
• No	131 (61.2)	29 (39.2)	45 (45.5)	30 (22.9)	

GP: general practitioner.

15% of these patients did not have rhinitis and 54% had mild rhinitis. Moreover, atopy, evaluated with a skin prick test, was not associated with rhinitis and with any parameter of asthma severity.[25] A very recent study confirms that the prevalence of allergic rhinitis is similar between patients suffering from limited-symptom or multi-symptom asthma, while multi-symptom asthma is closely related to chronic rhinosinusitis.[26]

Severity of the diseases seems relevant to explain the discrepancies between our result and that of Navarro et al.[9] In this survey the methodology for enrollment of patients (diagnosis performed by a specialist) was similar to our study, but the criteria differed in patient selection because allergic patients sensitized to any aeroallergen were included, while in our survey all patients were suffering from rhinitis and asthma associated with mite allergy, which is associated with severe disease patterns.[27,28] Indeed the overall lower severity of rhinitis and asthma found in the Spanish survey is well documented by the unbalance in the prevalence of the mild intermittent

Table 5 Patient-reported comorbidity by asthma severity grade.

	Intermittent asthma *n* (%)	Mild persistent asthma *n* (%)	Moderate persistent asthma *n* (%)	Severe persistent asthma *n* (%)	*p*
Sinusitis (516/518 pts)					
• Yes	19 (9.0)	10 (13.5)	13 (13.1)	26 (19.8)	0.039
• No	193 (91.0)	64 (86.5)	86 (86.9)	105 (80.2)	
Nasal polyposis (516/518 pts)					
• Yes	4 (1.9)	2 (2.7)	4 (4.0)	12 (9.2)	0.011
• No	208 (98.1)	72 (97.3)	95 (96.0)	119 (90.8)	
GERD (516/518 pts)					
• Yes	13 (6.1)	10 (13.5)	11 (11.1)	22 (16.8)	0.017
• No	199 (93.9)	64 (86.5)	88 (88.9)	109 (83.2)	
All comorbidities (518/518 pts)					
• Yes	29 (13.6)	17 (23.0)	21 (21.2)	44 (33.6)	<0.0001
• No	185 (86.4)	57 (77.0)	78 (78.8)	87 (66.4)	

GERD: gastro-oesophageal reflux disease.

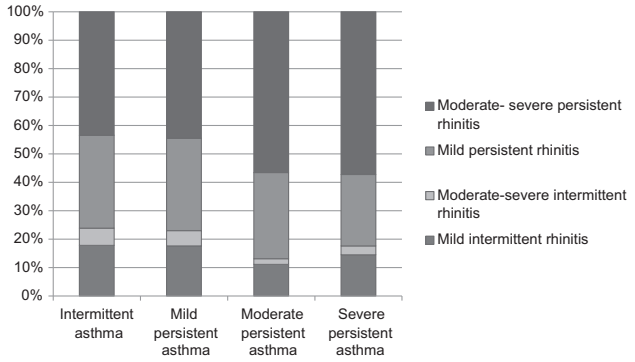

Figure 1 Percentage distribution of rhinitis severity according to the severity of coexistent asthma.

rhinitis subset (24%), which was higher than that in our survey (15.6%) and by the prevalence of moderate-severe persistent rhinitis (35%) which was lower than that in our survey (49.6%). Even more evident is the unbalance of severity in coexisting asthma: the prevalence of severe persistent asthma was 4% compared with 25% in our study.

A self reported diagnosis of chronic rhinosinusitis was recorded in 13% of our patients and this could affect the link between the severity of rhinitis and asthma of the survey. Since these patients met the inclusion criteria of the study and the interplay between mite allergic rhinitis and chronic rhinosinusitis is an open question,[29,30] they were included in the study anyway. However an evaluation, excluding this subset of patients was performed and the result of the survey did not change (data not shown).

Subjective assessment of rhinitis and asthma severity is the most questionable point of our study; a need for more sophisticated tools to investigate this relationship in mite allergic patients with respiratory allergy has been emphasized.[31] However our study aim was only to evaluate the relationship between asthma and rhinitis severity with those tools that are currently used in the clinical setting and in real life surveys.[8,9,11,27] Unfortunately, rhinitis and asthma severity assessment is not an easy task in real world. That is why both ARIA and GINA classifications were not designed as tools for epidemiological purposes, but rather for clinicians to provide an appropriate therapy according to disease severity levels.

Moreover the surveyed population, referring to a specialist, is probably emphasizing symptoms, at least for one of the diseases, therefore caution has to be used to generalize our deductions.

In conclusion, a complex association between the spectrums of respective severities of rhinitis and asthma was found. A statistically significant association between the increasing prevalence of the subset of patients with moderate-severe persistent rhinitis and increasing asthma severity was documented, but the amount of this increase was not great enough to change the spectrum of the rhinitis severity as whole. In our study the increase was 31%, possibly not enough to determine a clear association between severities as found instead in the survey in which this amount was more than 100%.[8] This is probably due to mite allergy, which is associated with severe disease patterns both for allergic rhinitis and asthma, in particular the high prevalence of moderate-severe persistent rhinitis patients even among the intermittent asthma group reduces the rate of increase of the severity of rhinitis across the increasing severity of asthma and questions the role of the allergic rhinitis severity as a marker of progressive involvement of the lower airways.

Further studies addressing the assessment of rhinitis and asthma severity will be necessary to better understand the link between upper and lower airway comorbidity.

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Conflicts of interest

The authors have declared that they have no conflicts of interest.

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