

The Characteristics of Severe Chronic Upper-Airway Disease (SCUAD) in Patients with Allergic Rhinitis: A Real-Life Multicenter Cross-Sectional Italian Study

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Keywords

Allergic rhinitis · Severe chronic upper-airway disease · Asthma · CARAT · Visual analogue scale

Abstract

Background: There are few studies regarding severe chronic upper-airway disease (SCUAD) that represents an important socioeconomic problem for the treatment of rhinitis and associated comorbidities, particularly asthma. **Objectives:** The aim of our study is to evaluate the prevalence of this pathology in patients with allergic rhinitis (AR) in real life, to phenotype allergic patients with SCUAD, and to identify which factors are related to the severity of the disease. **Methods:** We studied 113 patients with uncontrolled AR despite optimal adherence to therapy according to the Allergic Rhi-

nititis and its Impact on Asthma (ARIA) guidelines in a multicenter Italian study, analyzing comorbidity, use of additional drugs, not scheduled visits, and the number of emergency room admissions. **Results:** Our data suggest that polysensitization is the only statistically significant factor correlating with SCUAD. Asthma does not seem to represent a correlating factor. An important finding is the poor use (20%) of allergy immunotherapy (AIT), although patients were suffering from AR and the ARIA guidelines recommend the use of AIT in moderate/severe AR. **Conclusions:** The SCUAD population seems not to have a specific phenotype; there is a greater presence of SCUAD in polysensitized patients, perhaps a sign of greater inflammation. © 2019 S. Karger AG, Basel

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Introduction

The prevalence of allergic respiratory diseases and asthma is increasing worldwide, and the complexity and severity of such diseases continue to grow, especially in young subjects who are bearing the greatest burden. In Europe, approximately 23% of the population is affected by allergic rhinitis (AR) [1]. Furthermore, asthma represents a major health and socioeconomic concern, considering that more than 300 million people worldwide are currently affected by this condition. Moreover, AR is frequently associated with allergic asthma, and this increases the overall socioeconomic burden [2]. Despite effective therapies that are currently available, a considerable number of patients do not achieve a satisfactory disease control [3]. Although most patients with chronic upper-airway diseases have controlled symptoms during treatment, many patients have a “severe chronic upper-airway disease” (SCUAD) [4]. SCUAD defines those patients whose symptoms are inadequately controlled despite adequate pharmacologic treatment based on international and national guidelines. These patients have an impaired quality of life, social functioning, sleep, and school/work performance. Severe uncontrolled AR, non-AR, chronic rhinosinusitis, aspirin-exacerbated respiratory diseases, or occupational airway diseases are defined as SCUAD. Comorbidities are common in patients with SCUAD and might increase their severity. The concept of “control of disease” has only recently been introduced in the field of AR [5]. In case of poor control of symptoms despite guideline-directed pharmacotherapy, one needs to consider the presence of SCUAD but also treatment-related, diagnosis-related, and/or patient-related factors [6]. Furthermore, the prevalence of SCUAD in “real life” has not yet been extensively established. It seems that non-AR is the one that fits most in the SCUAD category, but data in the literature are scarce and not sufficiently established [4]. A recent study indicates that 20% of the subjects with AR are symptomatic despite prescribed therapy. It is, however, also true that when considering uncontrolled rhinitis, we must take into account various factors related to the severity of the disease itself and its comorbidities but also factors related to the patient (poor adherence to therapy), diagnostic errors, or inadequate treatments [6]. The aim of our study was to evaluate the prevalence of SCUAD in patients with AR. We have tried to analyze only the factors related to the severity of the disease and associated comorbidities, eliminating other confounding factors (i.e., poor adherence to therapy) as much as possible and trying to phenotype the AR patient affected by SCUAD.

Methods

This was a multicenter observational cross-sectional study involving patients with AR (≥ 18 years) referred to Allergy Centers of Italy (Brescia, Bari, Parma, Piacenza, Salerno, Turin, and Verona) between June and December 2017. Only patients with ascertained symptoms of AR were included. We assessed allergy sensitization using the skin prick test according to the European Allergy and Clinical Immunology Society recommendations [7] and considered “poliallergic” subjects with positive response to more than 2 allergens or subjects with positive response both to at least a seasonal and a perennial allergen. Among these subjects, the “real” SCUADs have been identified; in particular, patients who did not respond to the maximal level of therapy as indicated by the ARIA guidelines (association of topical nasal steroids and topical antihistamines; in some cases, antihistamines tablets or saline solution were added) [8] were selected, despite being compliant with the prescribed therapy and correctly using the drug. We carefully assessed that patients correctly used the nasal spray and that they regularly took the prescribed therapies.

Patients who said they were satisfied with the therapy with antihistamines (topical or systemic), saline solution, or topical steroids were not included in the study. Patients with AR associated with other diseases were not included.

These selected patients were asked to fill in a questionnaire specifying personal data, the onset time and duration of AR, the presence of mono- or polysensitization, the presence of comorbidities (in particular asthma, rhinosinusitis, and nasal polyposis) to try to identify the factor that could most influence the failure to control the AR. However, patients with AR who said they were satisfied with the prescribed therapy and had a good level of symptom control were not included in the study. The control level was assessed by the visual analogue scale (VAS; 0 = troublesome symptoms, 10 = no symptoms) [8]. As in recent data from the literature, patients with VAS >5 were considered uncontrolled, VAS 2–5 partly controlled, and VAS <2 well controlled [9]. If patients with AR were also asthmatics, the Control of Allergic Rhinitis and Asthma Test (CARAT) questionnaire was also completed [9]. CARAT is a tool created and validated to measure disease control of both AR and asthma. It is a self-administered questionnaire that quantifies not only nasal, ocular, oropharyngeal, lower-respiratory-tract symptoms, sleep impairment, activities, and psychosocial impediments but also treatment and exacerbation. The more the patient is symptomatic and has a poor quality of life, the lower the CARAT score [10]. In addition, the relevant demographic and clinical data (age, sex, duration of the disease, and allergen sensitizations) were recorded for the analyses. The type of medications (e.g., antihistamines, nasal steroids, or decongestants), their frequency of dosing, and possible incremental use were assessed.

Statistical Analysis

All statistical procedures were performed using the statistical package STATA version 14 for Windows (STATA®; Stata Corp -LP, College Station, TX, USA). In all tests, the significance was carried out at a 0.05 level. To test for heterogeneity, i.e., whether the estimated prevalence in all centers is the same, meta-analysis was performed. Heterogeneity is also quantified using the I-squared measure [11]. In the case of significant heterogeneity, all analyses were successively performed considering each center as a cluster random sample and adjusting consequently standard er-

Table 1. Demographic and clinical data of the patient population

Patients studied, <i>n</i>	113
Sex	
Female	56 (49.6)
Male	57 (50.4)
Age	
16–20 years	17 (15)
21–40 years	36 (31.9)
41–60 years	43 (38.1)
61–80 years	17 (15)
Duration of AR symptoms	
<5 years	31 (27.4)
5–10 years	37 (32.7)
11–20 years	23 (20.4)
>21 years	22 (19.5)
Allergen monosensitization	32 (28.3)
Allergen polysensitization	81 (71.7)
Perennial allergen, <i>n</i>	104
Seasonal allergen, <i>n</i>	202
Presence of comorbidities	88 (77.9)
Coexistence of asthma	55 (48.7)
Coexistence of rhinosinusitis	58 (51.3)
Coexistence of nasal polyposis	34 (30)
ASA intolerance	17 (15)

Values are presented as *n* (%), unless otherwise stated. ASA, acetylsalicylic acid.

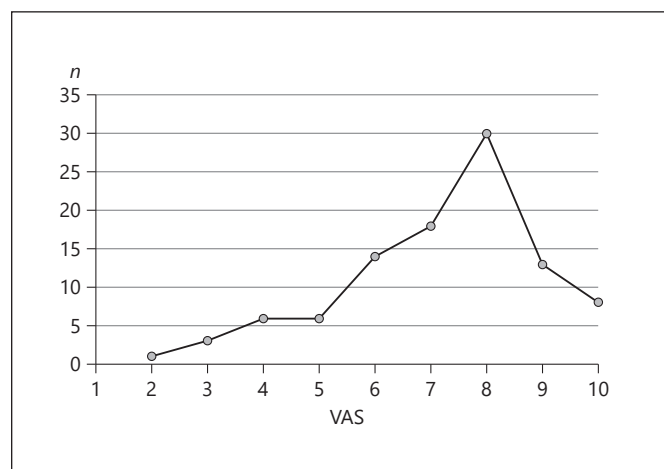
rors (SE) of the estimates. For the analysis of symptom severity and symptomatic treatment changes, the categorization “present always, never, less than or more than 2/week” was adopted. Age was categorized in 10-year intervals. The time of symptoms’ duration was classified as <1, 1–4, 5–10, 11–20, and >20 years. All categorized variables were used in the analysis as ordinal variables when appropriate. To investigate the relationship between allergy and VAS, we considered perennial (i.e., house dust mites, cat, dog) and seasonal (pollen) allergens separately. To investigate which factors could have influenced the VAS score, the relationship of the VAS score (dependent variables) and the number of positive allergens, single allergen positivity, symptoms, quality of life, and medication use, we used ordinal logistic regression, with VAS score quartiles as dependent variable, measuring the increase in the log odds of being in a higher level of the VAS score for a class increase in each predictive variable (i.e., going from 0 to 4), given all other variables in the model are held stable. The parallel regression assumption was tested by the Brant test [12, 13]. The predicted marginal probabilities of VAS ≥5 (in % scale) and VAS in the higher percentile were computed and reported. In all analyses, bootstrap estimation of SE was used [14, 15].

Results

In Table 1, the characteristics of the SCUAD population are reported.

Table 2. Socioeconomic impact of SCUAD and frequency in the use of systemic steroids in patients with SCUAD

Outpatient visits not scheduled for recurrent symptoms of rhinosinusitis in the last year	82 (0.73 visits per patient/year)
Emergency room access for recurrent symptoms of rhinosinusitis in the last year	8 admissions out of 113 patients (0.07 admissions per patient/year)
Hospital admissions for recurrent symptoms of rhinosinusitis in the last year	5 admissions out of 113 patients (0.04 hospitalizations per patient/year)
Number of cycles of systemic steroids for recurrent symptoms of rhinosinusitis in the last year	153 cycles (1.35 cycles per patient/year)

**Fig. 1.** Frequency distribution of VAS.

The prevalence of SCUAD was 6.8%, varying from 2.9 to 20% according to the different centers involved. The analysis of heterogeneity between centers gave nonsignificant results (heterogeneity $\chi^2 = 12.38$ [df 08]; $p = 0.089$ [variation in SE attributable to heterogeneity 43.4%].

The VAS score varied from 2 to 10 with an average of 7.17 (data indicate that the rhinitis population was not controlled; Fig. 1).

The CARAT score varied from 6 to 28 with an average of 17.3 (data indicating that asthma was better controlled than rhinitis). Asthma was present in 55 patients (49%), and 24 (21%) suffered from asthma level 3–5. Nasal polyposis was present in 34 patients (30%), and sinusitis in 58 (51%). Eighty-one patients (72%) were polysensitized [16].

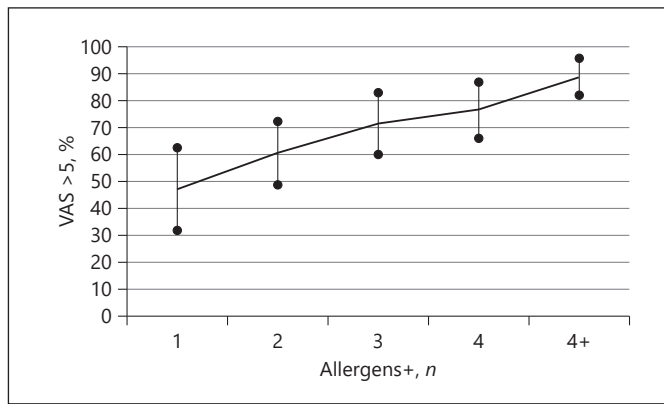


Fig. 2. Probability of VAS > 5 in relation to the number of positive allergen reactions.

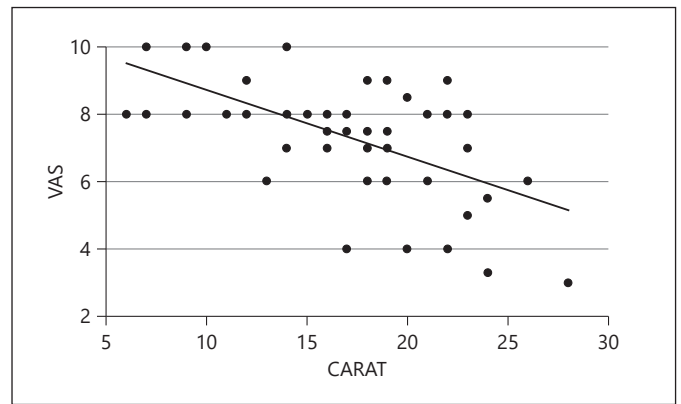


Fig. 3. Relationship between VAS and CARAT in 42 patients with AR and comorbid asthma.

Table 3. Results of ordinal logistic regression with VAS quartiles and number of allergen positivities as predictive variables, adjusted for the type of allergy

Number of allergens	Odds ratio	95% CI		<i>p</i> > z
-1	1			
2	2.418	0.739	7.913	0.144
3	5.817	1.157	29.242	0.033
4	9.187	1.363	61.916	0.023
4+	52.692	2.591	1,071.715	0.010

Nasal cytology, even if it is a useful tool to diagnose mixed rhinitis difficult to treat, has been used for the diagnosis of rhinitis in only 30 patients (27% of the patients evaluated).

Because of the poor symptom control, 82 unscheduled outpatient visits, 8 emergency room admissions, and 5 hospital admissions were performed. Treatment with a cycle of systemic steroids was also required in 153 cases (Table 2).

AIT was prescribed to 23 patients (20%); of these, 7 (30%) used subcutaneous immunotherapy treatment and 16 (70%) sublingual immunotherapy; 9 patients (39%) for perennial allergens, and 14 (61%) for seasonal allergens.

Table 3 shows the results of ordinal logistic regression with *p* 95% CI using VAS quartiles and number of allergen positivities as predictive variables concurring with specific allergen positivity. The Brant test of parallel regression assumption was not significant at the 5% level (*p* = 0.45). The relative risk of being the higher percentile

versus the lower one of VAS (less control) increases with the number of allergens (significantly more than 2).

Figure 2 shows the probability of VAS > 5 for the number of positive allergen reactions estimated by means of ordinal logistic regression.

No other factors seem to influence AR control. Figure 3 shows the relationship between VAS and CARAT among 42 patients with AR and comorbid asthma.

Discussion

This is one of the first SCUAD polycentric studies in “real life”.

In literature there are only few data about SCUAD and its prevalence is about 20% without making a difference between allergic and non-AR [4].

First, we noticed a prevalence of SCUAD in AR of 6.8%. Such a low prevalence could be due to the fact that we “only” analyzed allergic patients and, according to the literature, the patients most difficult to treat are those affected by chronic rhinosinusitis with or without nasal polyps. Moreover, even if they were optimally adherent to therapy, only patients who could not be controlled were considered SCUAD patients.

We observed that this low prevalence of SCUAD is very similar to that found in asthmatics with severe asthma, so we could compare SCUAD in rhinitis patients with severe asthma in asthmatic patients.

The SCUAD population from our data seemed not to have a specific phenotype: the frequency of asthma, polypsis, and sinusitis was similar to that found in AR data from the literature (independently of the control).

The interesting data is the greater presence of SCUAD in polysensitized patients, which perhaps is a sign of greater inflammation in these subjects compared to the monosensitive ones. Moreover, the poor control does not correlate with the type of allergen (perennial or seasonal) but in a linear way with the number of allergens.

In patients with SCUAD and asthma, we observed that asthma was better controlled than rhinitis (the median CARAT value was 17.3, indicating a moderate control of the disease), but we found a direct relationship between asthma control and AR control (Fig. 3). This is important from a practical point of view because in patients with united airway disease, the control of the upper airways could influence lower-airways control.

Concerning therapeutic aspects, we observed a limited use of AIT (only in 20% of the patients) despite guideline recommendation.

Finally, SCUAD has also an important socioeconomic impact as documented by unscheduled visits and the cycles of systemic steroids.

Statement of Ethics

Since the procedures used are part of standard care and no intervention was done, this study did not require informed consent or approval by the appropriate ethics committee.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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None to declare for all authors.

Author Contributions

All authors equally contributed to the clinical work, collected the data, and drafted the manuscript. All authors read and approved the final manuscript.

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