Severe asthma phenotyping: the applicability of current proposols in daily practice

Abstract

Background: Severe asthma (SA) is also need to be phenotyping. We aimed to demonstrate the applicability of current definition and classification proposals in daily practice.

Methods: SA patients, according to WHO definition of treatment resistant SA, were enrolled from the allergy clinic. The SARP algorith define and WHO proposal were applied to the subjects independently by asthma experts. Demographic and clinical characteristics of the subjects were used for the comparison.

Results: Ninety-five (F/M: 68/27) patients with a mean age of 45.97±9.44years (range25-71) were enrolled. The patients were grouped as controlled treatment-resistant SA (56%) and uncontrolled treatment resistant SA group (44%). There was no statistically significant difference between the groups but aspirin hypersensitivity. 49% of patients was classified as exacerbates, 26% as fixed airway obstruction group and 23% as undefined (other 2%). Age and mold sensitivity was higher; FEV1/FVC and FEF25-75 were lower in exacerbation-prone SA. More than half of the patients were define clustered at 4 and 5 according to SARP proposol. Patients with fixed obstruction were only in the clusters 4 and 5.

Conclusion: Current phenotyping proposols failed to cover all SA patients. Thus, there is still need further investigations in order to explore validity and applicability of the phenotyping of SA.

Keywords: adult asthma, severe asthma, phenotype, cluster analysis, refractory asthma, difficult-to-treat asthma

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Introduction

Asthma affects 300million people of all ages in the world and the prevalence of asthma is increasing.[1] Fortunately, most patients with asthma have a mild-to-moderate disease and can be controlled with optimal treatment. Around 10% of the overall asthmatics suffer from ongoing symptoms, frequent exacerbations and reduced quality of life despite appropriate therapy. The cost of illness related to asthma is extremely high, and more than 50% of the asthma patient care costs are attributed to asthma cases with ongoing symptoms due to unscheduled health care utilization, hospitalizations and the cost of pharmacotherapy.[2,3] Thus, in recent years, scientific attention mostly has been focused on the severe asthma (SA).

Various definitions have emerged to characterize the clinical features of SA, but essential feature of this phenotype is the need for high doses of inhaled corticosteroids plus long-acting bronchodilators to achieve disease control.[4] European Respiratory Society defined the term *difficult* asthma in 1999, and subsequently American Thoracic Society defined the term *refractory* asthma. Later an ERS workshop statement on SA has defined the disease as being reserved to those patients who have *refractory* asthma despite extensive reevaluation over a 6-month period. In 2009, the World Health Organization (WHO) proposed a global definition of SA. The new classification identifies three broad categories of SA: untreated SA, *difficult*-to-treat SA and treatment-resistant SA.[5]

Several multicenter cohort studies of SA patients have been published. The ENFUMOSA study was a multicenter European observational study comparing 163 subjects with SA and 158 patients with asthma controlled on low-dose ICS and demonstrated that SA may be characterized by small airway diseases[6] as is all RAD. The TENOR study, including 4756 patients from 283 sites, sought to establish characteristics of patients with very poorly controlled asthma over a 2year observational period in the United States and identified allergic sensitization, post bronchodilator lung function, the use of nonprivate health care insurance, and treatment by a pulmonologist as significant and independent predictors of having consistently very poor controlled asthma over a 2year period.[7] Another US multicenter cohort study (SARP) establish that SA patients were older, had a longer duration of disease, and had more frequent emergency health care utilization.[8] The UK Severe Asthma Network (382 patients from 4 centers) has identified the importance of intercenter variation in clinical characteristics such as more preserved lung function in Asian ethnicity and greater allergic sensitization to house dust mite in London than the other centers.[9] In other words, both European and North American severe asthma cohorts strongly support the presence of different subgroups or phenotypes.[10]

Phenotyping of SA becomes an essential element of the new approaches for personalized management. Despite significant interest demonstrated by specialists, most physicians are unable to fully understand the clustering process, and its translation in the real world to treat asthma is not clear.[11] In this study, the main purpose was classified SA patients according to WHO definition, and the secondary aim was to compare phenotypes by using both clinical presentation and SARP clustering system in order to observe the manifestation of daily clinical practice.

Materials and methods

Study population

In this retrospective study, 95 patients with a diagnosis of treatment-resistant SA according to WHO universal definitions were enrolled at the Department of Allergic Diseases at our center between 2006 and 2011. Patients under 18years and/or with lung disease other than asthma were excluded. Patients were consecutively collected from subjects admitted to the department due to uncontrolled asthma despite being prescribed high levels of asthma medications. Before the enrollment, all patients were reevaluated by asthma experts certified in both pulmonology and allergic diseases. A standardized questionnaire based on demographic characteristics, asthma control and severity, and medication use was administered to all participants. For the initial visit, detailed personal and familial history, physical examination, diagnostic tests, chest radiography, spirometry with bronchodilator test, allergy skin testing, lab tests (IgE, peripheral eosinophil count), assessing inhaler technique, triggers and comorbidities were evaluated. Follow-up visits were performed with 4-6weeks intervals at least for 6months. When necessary, computerized tomography scans of the chest were taken and consulted for comorbidities with related disciplines: ENT, polysomnography, gastroenterology, psychiatry, radiology, interventional bronchology.

Pulmonary function tests

Spirometry was performed by trained respiratory technicians using a flow-sensor spirometer (Sensormedics, Vmax 229, Yorba Linda-California). Pre-bronchodilator spirometry was performed for baseline % predicted FEV1. We confirmed the patients had withheld medication appropriately prior to testing. Post-bronchodilator spirometry was obtained after salbutamol (400mcg) administration and was defined as maximal % predicted FEV1. Reversibility was defined as a 12% change in FEV1.

Evaluation of atopy

Atopy was defined as a positive skin test to at least one of the aeroallergens. Glycerinated extracts of house dust mites, cockroach, molds (aspergillus, alternaira, cladosporium, penicllium), cat and dog epithelia, grass, tree and weed pollen antigens were used (Stallergenes, Antony/France). The puncture method with a 1mm tip disposable lancet was used, and a wheal reaction with a mean diameter of 3mm greater than the negative control was accepted as a positive response.

Phenotyping

All patients were in the group 3 (treatment-resistant SA) of WHO severe asthma definition. Later, patients were assigned to the two subgroups. Group A consisted of patients in which control could be maintained, group B consisted of patients in which control was not achieved.[5] Secondarily, patients were clustered using three variables (baseline FEV1-with a bronchodilator withhold-, maximal FEV1 after six-to eight puffs of albuterol, and age of onset of asthma) as in SARP.[8]

Statistical analysis

The Statistical Package for Social Sciences (SPSS v.17; Chicago, IL, USA) was used to analyze the data. Numeric values were expressed as mean±SD and categorical/ordinal values as n(%) and results were expressed as the mean (95% confidence interval)±SEM. Nonparametric tests were used due to heterogeneity of the groups. Differences between study groups were examined by Kruskal Wallis test, and any significant differences were further analyzed by pairwise comparisons using Mann-Whitney U test. All directional p values were two-tailed, and significance was assigned to values lower than 0.05.

Results

A total of 95 patients, 68 female (71.6%) and 27 male (28.4%), with a mean age of 45.97±9.44years (25-71) were enrolled. 61(64.2%) patients had never smoked, and nearly 45% of all patients were obese. 33(34.7%) patients had aspirin hypersensitivity proved by ASA provocation test, 4(4.29%) have other drug hypersensitivities. 46(48.4%) patients had nasal polyps. 56(62.1%) were classified as non-atopic. The mean time to diagnosis was 11.41±7.9 (1-33years). The mean baseline FEV1 level was 1.45±0.53(0.45-3.01) L and 49.43±13.9(21-83) % predicted. 47(49.5%) patients were taking more than 3 drugs. Of the 95 patients, 45 patients were hospitalized more than twice per year. The demographic and clinical details of the study population are summarized in Table 1.

Table 1 Demographics and clinical characteristics of study population (n=95)

Sex, n (%)	
Female	68(71.6%)
Male	27(28.4%)
Age	
Mean ±SD(min-max), years	45.97±9.44(25-71)
Asthma duration	
Mean ±SD(min-max), years	11.41±7.9(1-33)
Smoking Status, n (%)	
Never smoker	61(64.2%)
Ex-smoker	29(30.5%)
Active smoker	5(5.39%)
Drug Allergy, n (%)	
None	58(61.1%)
ASA hypersensitivity	33(34.7%)
Others(antibiotics, RCM)	4(4.29%)
Nasal Polyp, n (%)	
No	49(51.6%)
Yes	46(48.4%)
Obesity Status, n (%)	
Normal	20(21.1%)
Overweight	31(32.6%)
Obese	40(42.1%)
Morbid obese	4(4.2%)
Atopy Status, n (%)	
Nonatopic	56(62.1%)
Atopic	36(37.9%)
House dust mites sensitivity	27(75%)
Moulds sensitivity	12(33.3%)
Cat sensitivity	7(19.4%)
Cockroach sensitivity	3(8.3%)
Pollen sensitivity	12(33.3%)
Baseline FEV1	
Mean ±SD(min-max), L	1.45±0.53(0.45-3.01)
Mean ±SD(min-max), % predicted	49.43±13.9(21-83)

Table Continued..

Baseline FEV1	
Baseline FEV1	
Medications used, n (%)	
ICS	95(100%)
LABA	95(95%)
LTRA	89(93.7%)
Theophylline	27(28.4%)
Oral CS	6(6.3%)
Anti IgE	9(9.5%)
ASA desensitization	17(17.9%)
≠ **of Medicaitons used, n (%)**	
3	48(50.5%)
>3	47(49.5%)
≠ **of Hospitalization for Asthma, n(%)**	
0	27(28.4%)
1	23(24.2%)
≥2	45(47.4%)

The study group was clustered as follows: 56% of the patients were in the group A (controlled treatment-resistant SA), 44% of the patients were in group B (uncontrolled treatment-resistant SA). There

was no significant difference between two groups according to age, gender, age at diagnosis, smoking status, obesity, nasal polyposis, atopy, parameters of PFT or the number of drugs used. Aspirin hypersensitivity was significantly higher in group B (Group A/Group B: 30.3%/69.7%) (p=0.048) (Graphic 1).

According to clinical phenotypes, the patients were divided into three groups. 49% of patients had frequent exacerbations, 26% of patients had irreversible obstruction according to FEV1 and 23% of undefined or did not have these 2 criteria? There was no significant difference between groups with respect to gender, age at diagnosis, cigarette smoke, obesity, drug hypersensitivity, atopy, the amount of drugs used. Age was significantly higher in exacerbation-prone severe asthma group. Analysis of lung function revealed that FEV1/FVC and FEF25-75 were also lowest in this group. Mold sensitivity was higher in the exacerbation-prone severe asthma group. Aspirin hypersensitivity was higher in the undefined group (Table 2). 63% of exacerbation-prone SA patients were in treatment resistant asthma group B according to WHO.

Using the SARP algorithm, SA patients were clustered as follows. 2.1% of subjects (n=2) are grouped into cluster 1. 31.6 (%) (n=30) of subjects are grouped in Cluster 2. 10.5% (n=10) of subjects are grouped in Cluster 3. Cluster 4 was the largest group (n=32; 33.6%). The remaining 22.1% (n=21) of patients assigned into cluster 5. The patients who had fixed obstruction was only at clusters 4 and 5.

Table 2 Comparison of features of SA patients according to clinical presentation

Age*, y	45.63±9.26	51.12±9.35	41.25±7.29
FEV1 min L£	1.45±0.46	1.14±0.37	1.77±0.61
FEV1 min %#	50.13±14.45	43.04±9.61	55.00±14.76
FEF25-75 min ∞	30.46±15.07	20.7±7.52	32.63±16.39
Mold sensitization, n	11	1	-
ASA tolerant, n	33	17	8
ASA intolerant¥, n	11	7	15

*Exa. vs fixed 0.05
Exa. vs unclassified 0.031
Fixed vs unclassified <0.001
£Exa. vs fixed 0.004
Exa. vs unclassified 0.049
Fixed vs unclassified <0.001
#Exa. vs fixed 0.04
Exa. vs unclassified >0.05
Fixed vs unclassified 0.004
∞Exa. vs fixed 0.007
Exa. vs unclassified 0.007
Fixed vs unclassified <0.001
¥Unclassified vs exa. and fixed 0.04

Discussion

In the current study, according to WHO clinical phenotyping system 23% of the SA patients were not able to be classified. Using the SARP clustering system, 1/3 of the patients clustered in group 2 with normal lung functions and more than half of the patients were clustered in group 4 and 5 with female predominance, decreased lung functions and non-atopic status. Thus two different classification schemes for SA failed to cover all SA in daily clinical practice.

Asthma, and SA in particular, is increasingly recognized as a heterogeneous disease. Many definitions have been used for

SA[3,7,8] and also many previous studies have attempted to define phenotypes of severe asthma.[5,6,9] Phenotypes may be divided into 2 main categories such as clinical phenotypes and inflammatory phenotypes,[10] According to clinical features the 3 most relevant clinical phenotypes are exacerbation prone SA, SA with fixed airflow obstruction and oralcorticosteroid-dependent SA.[11] Patients with frequent exacerbations are susceptible to exacerbations as a result of modifiable and nonmodifiable risk factors.[12] Fixed obstruction is probably related to bronchial inflammation, which worsens after exacerbations and airway remodeling.[13] Childhood-onset, female gender, smoking and genetic predisposition are the most important risk factors contributing to developing fixed obstruction phenotype.

Several possible mechanisms have been suggested to explain corticosteroid-dependent SA.[14] The inflammatory phenotypes were defined according to inflammatory markers and cells by using noninvasive methods such as induced sputum, peripheral blood, urine, exhaled NO and electronic noses.[15] Three inflammatory phenotypes have been described; persistent eosinophilic SA, noneosinophilic SA with increased neutrophils and paucigranulocytic SA. Several studies have demonstrated eosinophilic or noneosinophilic inflammation in asthma by using pathobiologic characteristics to guide asthma management.[16,17] But some of these features may not always obtainable in clinical settings.

It is more important to classify asthma according to clinical presentation, pathophysiologic characteristics, and response to treatment. These features include lung function level, age of onset, triggering factors, frequency and severity of exacerbations, comorbidities, site of inflammation, remodeling changes and airway smooth muscle dysfunction. The Severe Asthma Research Program (SARP) performed cluster analysis of severe persistent asthma patients using 34 variables and defined five clusters. They also developed a simplified SARP algorithm for sorting based on three variables available in the clinical setting (baseline percent of predicted FEV1, maximal % predicted FEV1, age of asthma onset).[6]

Recently, 6 asthma endotypes have been demonstrated of which at least 4 are relevant to severe asthma. These 4 endotypes are early-onset severe allergic asthma, late-onset persistent eosinophilic asthma, aspirin exacerbated airway diseases and allergic bronchopulmonary mycoses.[18] Similarly (in this context), Amelink et al also confirmed that obese adult-onset asthma phenotype is not associated with eosinophilic airway inflammation and responsiveness to ICS but is characterized by poor asthma control, low quality of life and high health care utilization.[19] In the current study, we used cluster analysis to identify five clusters of SA and we compared the phenotyping according to clinical features (irreversible obstruction and exacerbation-prone severe asthma). Cluster 1 was the smallest (2,1%) group, differing from SARP. In clusters 1 and 2, half of the patients were atopic and had normal lung function. Cluster 2 subjects had early-onset asthma. Cluster 3 was a group of older, obese, mostly female subjects who were shown to have mild airway obstruction. This group was similar to that described in SARP and with the group of obese subjects with late-onset asthma.[6] Cluster 4 was the largest group and was predominantly female, non atopic, decreased lung function and early onset. Cluster 5 was late onset, non atopic, predominantly female and lowest lung function. These findings are similar to results of Amelink et al.[19]

Two unexpected results of the study were lower atopy rates and more female predominanc than those of the previous studies.[6,9] The most attractive finding of the study is that the majority of ASA hypersensitive patients were classified as neither exacerbation-prone nor fixed airway obstruction group. Thus, it may suggest that ASA hypersensitive SA is distinct clinical phenotype. Another striking result was that being elderly and having mold sensitivity, unrelated to obesity and gender, were found to be distinctive features of exacerbation-prone phenotype.

Although the present study was designed and conducted in tertiary allergy clinic by experienced asthma experts, it still has some limitations. First, the number of subjects is small. Second, we did not use path biological features for end typing due to the retrospective nature of the study.

In conclusion, the present study shows that actual classification/phenotyping/clustering proposals for severe asthma will miss characterizing some individuals in this group of patients. It is well known that asthma is heterogeneous disease and even SA comprises various clinical and path physiological phenotypes. Improved characterization of the disease could contribute to improved selection of appropriate treatment and a greater understanding of its path physiology and natural history. The results of ongoing studies such as "Unbiased Biomarkers for the Prediction of Respiratory Diseases" Outcome (U-BIOPRED) consortium should contribute to more detailed phenotyping of severe asthama.[14]

Acknowledgements

Conflict of interest

The author declares no conflict of interest.

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