

Factors leading to refractory asthma in patients from Saudi Arabia

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Abstract:

AIM: The aim of this study was to study the clinical characteristic of patient with refractory asthma (RA) from Saudi Arabia.

METHODS: This paper prospectively studied in a university hospital factors leading to RA in a cohort of patients who have inadequately controlled asthma or with frequent exacerbations despite optimum controller therapy. It also studied patients with asthma that requires extended periods of oral steroids to control.

RESULTS: The mean age was 45.1 years (± 9.1) where 74 patients were enrolled in this study with the age group (37–48 years) is having the highest percentage (64.8%). Female patients represented 62.2%. The two major comorbid conditions were allergic rhinitis (54.1%) and gastroesophageal reflux (33.8%). The vast majority (72 patients) had at least one trigger factor for asthma (97.3%). The asthma control test showed that 86.4% had an uncontrolled status. Spirometry showed mild disease in 9.5%, moderate in 47.3%, and severe in 43.2%. Eosinophilia was seen in only 16.2%. Immunoglobulin E level between 70 and 700 $\mu\text{g/L}$ was found in 58.1% of patients.

CONCLUSION: RA has certain clinical characteristics and associated comorbid conditions as well as precipitating factors that facilitate the identifications of these cases.

Key words:

Asthma, difficult-to-treat asthma, refractory asthma, Saudi Arabia

Refractory asthma (RA) is a heterogeneous condition that has no consensus on its definition and has been described in different terms such as difficult-to-treat asthma, difficult-to-control asthma, steroid-resistant, and steroid-dependent asthma.^[1,2] These terms are more of a descriptive nature rather than a reflection of phenotypes or pathological processes. Patients with RA have persistence of asthma symptoms that requires high doses of inhaled corticosteroids (ICS) in addition to long-acting beta 2 agonist agent (LABA) and other controller agents, or use of near-continuous oral steroid treatment to maintain asthma control.^[3,4] Before labeling a patient as a case of RA, there are factors that should be considered.^[5-10] Nonadherence to medications and poor technique of using inhalers are common preventable causes of uncontrolled asthma. There are also some comorbidities that are known to worsen asthma control and lead to the status of RA that includes chronic sinusitis, gastroesophageal reflux disease (GERD), sleep apnea syndrome, obesity, and congestive heart failure.^[11] Although RA affects approximately 5%–10% of asthmatic patients, its indirect cost represents approximately half of the total budget for asthma treatment.^[12,13] Most of this cost is related to patients with severe and/or RA, especially those requiring frequent emergency department visits and hospitalizations. Furthermore, the

presence of allergens at home or work, active or passive smoking, and psychosocial problems are other confounding factors that need special consideration.^[9] Moreover, lack of proper clinical assessment may lead misdiagnosis of asthma with other conditions such as bronchiectasis, endobronchial tumors, vocal cord dysfunction, and allergic bronchopulmonary aspergillosis.^[9,14] Psychosocial influences are likely to significantly contribute to the development of poorly controlled asthma; specifically, emotional and social stresses that have been shown to be associated with various indices of impaired airway functioning.^[15] These data indicate that these cases need special attention to identify

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their clinical characteristics. To the authors' knowledge, there are only scanty data that specifically address factors that lead to RA from Saudi Arabia. Therefore, the aim of this paper was to study the clinical characteristic of patients with RA from Saudi Arabia.

Methods

This paper prospectively studied a group of consecutive patients with the diagnosis of RA who fulfilled the eligibility criteria. It was conducted at King Khalid University Hospital, Riyadh, Saudi Arabia from January to December 2014. The approval of the Institutional Review Board was obtained from College of Medicine at King Saud University, Riyadh, Saudi Arabia. Patients with the diagnosis of asthma who have one of the following situations were included: A patient is inadequately controlled on combination therapy of ICS/LABA with other controllers such as long-acting anticholinergic agents or leukotrienes modifiers; a patient who has taken oral steroids for extended periods to control symptoms despite adequate standard treatment; or frequent exacerbations with emergency department visits or admissions despite adequate standard treatment. Exclusion criteria included the presence of any other known pulmonary disease including a prior diagnosis of chronic obstructive pulmonary disease (COPD), history of smoking, and presence of other major comorbid disease that might affect asthma disease activity such as metastatic cancer, collagen vascular disease, or congestive heart failure.

The demographic features and comorbidities associated with asthma, as well as triggers that may precipitate attacks were studied to identify the characteristics of patients with RA. The asthma control test (ACT) score and forced expiratory volume in 1 s (FEV_1) by spirometry were obtained during a patient visit to the out-patient clinic. Abnormal finding in paranasal sinuses (PNS) X-rays were also identified. Furthermore, abnormally high level of eosinophils, immunoglobulin E (IgE) level, and schistosoma titer was investigated. The ACT was defined as controlled when the score was ≥ 20 , partially controlled when the score was 16–19, and uncontrolled when the score was < 16 .^[16] Eosinophilia was defined as an absolute count of > 500 cells per microliter (cells/ μL).^[17] Based on FEV_1 , asthma severity was defined as mild when FEV_1 is $> 80\%$, moderate when FEV_1 is 60%–80%, and severe when FEV_1 is $< 60\%$.^[18]

Statistical Package for Social Sciences program IBM SPSS Software 2009 SPSS V 16.0 (SPSS Inc., Chicago, IL, USA) was used for data entry and analyses. Descriptive analyses were conducted by calculating the mean and standard deviation for the continuous variables and number and percent for categorical ones.

Results

The demographic characteristics of 74 patients enrolled in the study are shown in Table 1. The mean age was 45.1 years (± 9.1). The highest percentage was 36.5% for patients aged 49–60 years followed by age group 37–48 years with a percentage of 28.3%. The ratio of female to male was 1.64:1 with female and male patients representing 62.2% and 37.8%, respectively. City dwellers represented 77% of the patients, whereas only 17% came for villages or towns. Only 9% of patients with RA were

professionals by occupation. Office workers and teachers represented the largest group of 48.6%, whereas 20.2% were unemployed. Relevant comorbidities are shown in Table 2 where allergic rhinitis and GERD represent the two major factors with a percentage of 54.1% and 33.8%, respectively. A striking finding that 72 patients (97.3%) had at least one trigger factor for asthma.

Table 3 shows the results of laboratory and radiological findings. The ACT showed 86.4% had uncontrolled asthma. Spirometry showed mild disease in 9.5%, moderate in 47.3%, and severe in 43.2%. Eosinophilia was seen in only 16.2%. An IgE level between 70 and 700 $\mu\text{g/L}$ was found in 58.1%; however, one-third of patients had a level > 700 $\mu\text{g/L}$. A positive schistosoma titer was found in three patients only indicating current or past infection.

Discussion

This study showed that patients with RA from Saudi Arabia have certain clinical characteristics, associated comorbid conditions and precipitating factors that facilitate the prediction of this disease entity. Some of these factors are treatable

Table 1: Demographic characteristics of the study population (n=74)

Variables	n (%)
Mean age	45.1 \pm 9.1
Age (years)	
12-24	11 (14.9)
25-36	8 (10.8)
37-48	21 (28.3)
49-60	27 (36.5)
>60	7 (9.5)
Gender	
Male	28 (37.8)
Female	46 (62.2)
Nationality	
Saudi	68 (91.9)
Non-Saudi	6 (8.1)
Residence	
City	57 (77.0)
Village/town	17 (33.0)
Occupation	
Professional	9 (12.2)
Office work and teacher	36 (48.6)
Student	7 (9.5)
Housewife	7 (9.5)
Unemployed	15 (20.2)

Table 2: Comorbidities and triggers associated with asthma

Disease	n (%)
Allergic rhinitis	40 (54.1)
GERD	25 (33.8)
NSAIDs use	3 (4.1)
History of smoking	1 (1.4)

GERD = Gastroesophageal reflux disease, NSAIDs = Nonsteroidal anti-inflammatory agents

Table 3: Results of laboratory and radiological tests

Laboratory tests	n (%)
Asthma control test	
Controlled	3 (4.1)
Partially controlled	7 (9.5)
Uncontrolled	64 (86.4)
Asthma severity based on spirometry	
Mild (FEV ₁ <80%)	7 (9.5)
Moderate (FEV ₁ 60%-80%)	35 (47.3)
Severe (FEV ₁ <60%)	32 (43.2)
Eosinophils	
Normal	62 (83.8)
High	12 (16.2)
Immunoglobulin E (µg/L)	
<70	6 (8.1)
70-700	43 (58.1)
>700	25 (33.8)
Schistosomal titer	
Positive	3 (4.2)
Negative	71 (95.9)
Para-nasal sinuses X-ray	
Normal	20 (27)
Presence of evidence of sinusitis	54 (73)

FEV₁ = Forced expiratory volume in 1 s

and/or controllable; hence, better control is achievable with appropriate workup and management. The inclusion criteria were deliberately set in an attempt to describe patients currently being treated for RA. Our findings showed that patients with RA tend to be middle-age and older with more predominance of the female gender. This finding is consistent with other studies.^[5,19] Female predominance has also been described in another study from Saudi Arabia where 60% were females.^[20] A study from The Netherlands revealed that their patients were middle-aged with female predominance that represented 60%.^[21] This has also been documented in another cohort of patients with RA and persistent airflow limitation from the USA where female represented 60% of the studied population.^[7] Most of the cases seen in our study were Saudi nationals who are city dwellers and holding office work or professionals. A study from the USA showed that 35% of patients with RA were educated at college level or higher and 41% are working full time.^[7] In the literature, RA is more frequent in lower social economic status.^[7] The contradicting result in our study may be explained by better access to tertiary care facilities for those patients with a better social status.

Although PNS radiography was abnormal in more than two-thirds of the sample, clinical rhinosinusitis is only manifested clinically in half of the patients. The finding in this study is consistent with a cohort of 100 patients from the UK where half of the patients reported rhinosinusitis.^[19] Another cohort of patients from the USA (The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study) revealed that such a finding is present in 68% of cases.^[7] Gastroesophageal disease is manifested in one-third of the patients. Both rhinitis and GERD were reported from the Netherlands with a prevalence of 27.5% and 26%, respectively.^[21] The two entities are known to be associated with RA, and their control is an essential step before

consideration of a higher step of treatment.^[1,2] The nonsteroidal anti-inflammatory drugs use was reported in 4.1% in our cohort, compared to 7.5% from the Netherlands. The majority of our patients reported environmental triggers for their disease. A cross-sectional study conducted in an allergy clinic in Jeddah, Saudi Arabia showed that 77% of patients had at least one allergen.^[20] In a cohort from the USA, 92% reported positive skin test with different types of allergen identified.^[7] Out of this cohort, 11% had one allergen while the rest showed allergy for more than one allergen. Although blood eosinophilia was not common, increased IgE was very common. The IgE level measured in our patients was higher than the cohort of patients from the Netherlands, the United Kingdom, and the USA.^[7,19,21] One-third of our patients had a level >700 µg/L. This could be explained by the more severe disease in our cohort than the aforementioned studies as manifested by lower pulmonary physiological measures. Our study has the limitation of lack of detailed evaluation of types of allergens, the specific IgE, and parasites identification. Such a finding has an implication that patients with RA require more detailed allergy evaluation. It has also another implication on the selection of therapy with anti-IgE agents once appropriate workup is done, especially those with higher IgE level as a challenging category with the inconsistency of recommended therapy in the literature.

It is not surprising that most patients have uncontrolled asthma as defined by ACT score <20. Poor control of asthma has been documented in different studies reflecting the impact of the disease on patients.^[5,19] Most of the data related to asthma control in asthma from Saudi Arabia are mostly conducted in children with variable prevalence.^[22,23] However, an asthma control survey was conducted in Riyadh that showed 95% were either partially controlled or uncontrolled.^[24] Another recent cross-sectional study from a University hospital in Jeddah revealed that 88% were uncontrolled.^[20] Furthermore, the majority has either moderate or severe disease as manifested by the result of FEV₁. The cohort in this study was collected in a tertiary care facility; hence, their disease severity is likely to be worse than what has been reported in the literature.^[5,19,25] Despite the fact that all our patients are nonsmokers, the possibility of overlap with COPD cannot be excluded in this cohort without more appropriate workup.

It is worth mentioning that this study has some limitations. The available data will not allow a more comprehensive cluster analysis to identify phenotypes of patients with RA in Saudi Arabia.^[26] Another limitation is the lack of a detailed evaluation of the source of allergen and determination of allergen type by either specific IgE testing of skin test for the allergen. Finally, although smokers were excluded from being enrolled in this study, it is a challenge to ensure that there is no contamination of patient cohorts with those with COPD that includes asthma-COPD overlap syndrome.

These limitations are notwithstanding the unique aspect of this study is that it addressed an area with scanty research related to RA in Saudi Arabia. RA has certain clinical characteristics and associated comorbid conditions and precipitating factors that facilitate the identifications of these cases for better asthma control. The finding of this study is consistent with those from other parts of the world in some aspects. It also showed some difference as manifested by the higher evidence of atopy and

demographics of patients. We believe that this study serves as a stimulus for further research of RA in Saudi Arabia.

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Conflicts of interest

There are no conflicts of interest.

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