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Difficult-to-Treat and Severe Asthma

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Abstract

Introduction: The purpose of this article is to describe the characteristics, comorbidities and phenotypes of patients with difficult-to-treat asthma (DTA) and severe asthma (SA).
Materials and Methods: Descriptive, cross-sectional study of patients evaluated at the Difficult-to-Treat Asthma Clinic of the Hospital Británico within the period of one year. We registered the age, gender and anthropometric data, age of diagnosis, FEV1 at the beginning of follow-up and previous exacerbations. We evaluated symptom control with the Asthma Control Test and the Asthma Control Questionnaire. We registered the comorbidities and evaluated the inflammatory profile of patients according to blood biomarker measurements and induced sputum sample.
Results: Forty patients, 20 DTA and 20 SA. There weren't any significant differences regarding age, BMI, age of onset of symptoms, symptom control or FEV1 at the beginning of follow-up. Crises were more common in SA patients. The most commonly found comorbidities were obesity, OSAHS and gastroesophageal reflux disease. Psychiatric disorders were more common in SA patients. The most commonly found phenotype was allergen-reactive TH2.
Discussion and Conclusion: it is not easy to classify both groups, and many times there are overlapping characteristics. Comorbidities are frequent in both groups: obesity, OSAHS and reflux disease are the most common conditions. Being able to identify the asthma phenotype in order to target the treatment.

Key words: severe asthma; difficult-to-treat asthma; comorbidities

Introduction

Asthma is defined as a heterogeneous disease, usually characterized by inflammation and chronic remodelling of the airways. It is marked by sibilance, dyspnea, chest tightness and cough that varies with time in terms of intensity, together with a limitation of the expiratory airflow. Inflammation of the airways is associated with obstruction and bronchial hyperresponse[1]. Most asthma patients can be adequately treated with a combination of inhaled corticosteroids (ICS) and bronchodilators, usually long-acting beta-adrenergic agonists (LABA)[2, 3]. However, there is a group of patients in whom it is difficult to adequately control the symptoms, regardless of the indicated treatment. Taking into account the reason for which the group can't be controlled, the clinical management guidelines define a subgroup as uncontrolled, difficult to control or difficult-to-treat asthma (DTA) that has difficulties in controlling the symptoms regardless of the medium or high doses of inhaled steroids and a second follow-up controller. This lack of control could be due to the presence of comorbidities, household or work exposure factors, disease refractoriness or simply non-adherence to treatment or wrong use of inhaled devices[1]. Patients included in the DTA group are those with severe asthma (SA), and without disease control, despite the fact that they receive the complete treatment and show right adherence and a suitable management of comorbidities[1]. It is estimated that patients with difficult to treat asthma account for approximately 17% of all asthmatic patients; and 3.7% are severe asthmatics, representing 60% of asthma-related healthcare costs[1, 4].

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In the clinical practice it is difficult to make a categorical differentiation between patients with DTA and SA, since many comorbidities and exposure factors that would imply poor control of asthma are prevalent in the asthmatic population and are sometimes difficult to solve. It is common to find a division between both groups only if symptoms get to be controlled. The purpose of this work is to describe the characteristics, comorbidities and phenotypes of patients with DTA and SA.

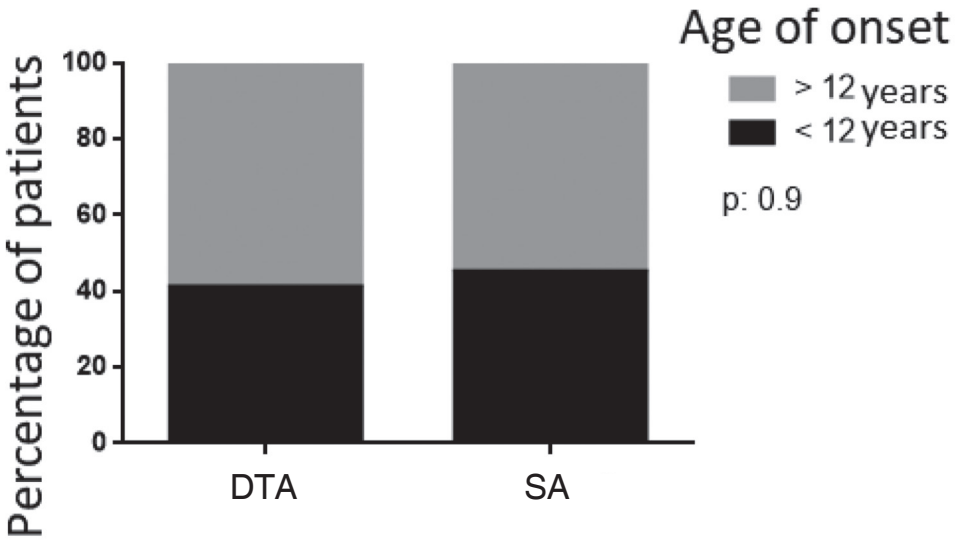
Materials and Methods

Descriptive, cross-sectional study of patients evaluated at the Difficult-to-Treat Asthma Clinic of the Hospital Británico from July 2018 to July 2019. The study included patients older than 18 years and those who met the difficult-to-treat and severe asthma criteria according to the GINA 2019 guidelines[1]. We registered age, gender and anthropometric data. We evaluated symptom control with the Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ) in the first consultation. Asthmatic exacerbation was defined as episodes characterized by the worsening of the respiratory symptoms with increased dyspnea, cough, sibilance or chest tightness and progressive loss of the pulmonary function and those requiring some modification of the regular treatment. It was defined as frequent exacerbation if there were ≥ 2 per year and severe exacerbation if the patient required hospitalization[1]. We registered the comorbidities including: obesity, patients with a body mass index (BMI) ≥ 30 kg/m^2, active smoking, obstructive sleep apnea-hypopnea syndrome (OSAHS) defined by the presence of an apnea-hypopnea index (AHI) ≥ 5, measured by respiratory polygraphy or polysomnography in sleep laboratories[5], rhinosinusitis and nasal polyps diagnosed by tomographic studies or previous surgery. The diagnosis of gastroesophageal reflux disease (GERD) was established by the presence of symptoms and/or when proven by digestive endoscopy; and the history of psychiatric disorders was determined by the evaluation carried out by the mental health team or by the presence of a previous confirmed diagnosis. We evaluated the inflammatory profile of the patients according to blood biomarker measurements, and in patients with SA we took induced sputum samples, defining them as type 2 inflammation if they showed blood eosinophilia ≥ 150/mm^3 and/or eosinophil count ≥ 2% in the sputum sample[1, 4, 6, 7]. Patients not fulfilling this criteria with more than 40% neutrophil cell count in the sputum sample were called neutrophilics[7]. Also, the measurement of serum IgE > 100 UI/l was considered elevated. This was found in patients with allergic asthma. We recorded the medication used in both groups.

In the statistical analysis, results were presented as percentages. For the numerical variables, results were shown as mean or standard deviation (SD). The Mann-Whitney or Chi Square Tests were used to compare differences between both groups. The results were analyzed with Prism 8 software (Graph Pad, La Jolla, CA).

Results

40 patients were included in the study for a period of one year, 20 of which met the criterion for difficult-to-treat asthma (DTA), and 20 for severe asthma (SA). The mean age was 57 ± 17.62 in DTA patients and 56 ± 15.47 years in SA patients. The mean BMI was 31.43 ± 7.47 and 30.23 ± 5.92 kg/m^2 respectively, with no significant differences in any of the variables. We discriminated the mean age of the asthma diagnosis in both groups, which was 24 ± 21 years for the DTA group and 26 ± 22 for the SA group. The diagnosis before 12 years of age accounted for 40% of the DTA patients and 45% of SA patients (p= 0.9) (**Graphic 1**). The mean result of the ACT questionnaire at the beginning of the follow-up was 15.33 ± 6.31 in DTA and 13.41 ± 4.38 in SA (p = 0.35); and the ACQ results were 1.89 ± 1.74 and 2.11 ± 1.56, respectively (p = 0.5), no significant differences were found. In the functional evaluation, the mean FEV_1 percentage at the beginning of the follow-up was 57 ± 13% in DTA and 50 ± 13% in SA (p = 0.1) (**Table 1**). Seventy percent of SA and 60% of DTA had had previous hospitalizations, non-significant difference were found (p = 0.08), (**Graphic 2**). 55% of SA patients and 20% of DTA patients had frequent crises, significant difference (p = 0.02) (**Graphic 3**). One hundred of patients with SA



Graphic 1. The diagnosis was made before 12 years of age in 40% of patients with DTA and 45% of patients with SA

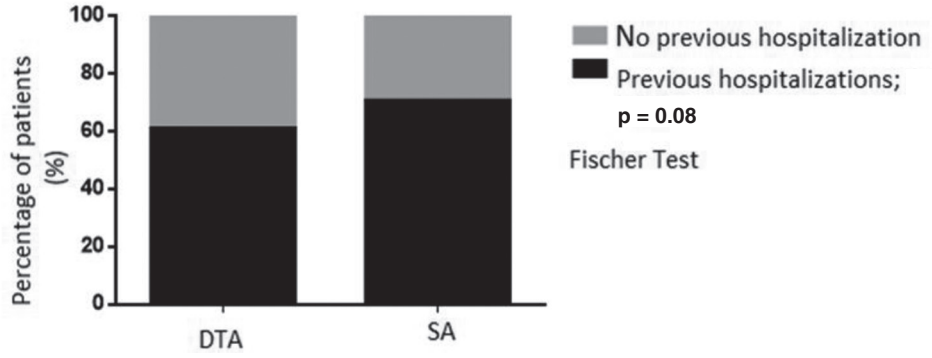
TABLE 1. Characteristics of patients with difficult-to-treat and severe asthma

	DTA	SA	*p*
Age years/ SD	57 ± 17.62	56 ± 15.47	0.78
Age of diagnosis years/SD	24 ± 21	26 ± 22	0.90
BMI kg/m²/SD	31.43 ± 7.47	30.23 ± 5.92	0.90
ACT/SD	15.33 ± 6.31	13.41 ± 4.38	0.35
ACQ/SD	1.89 ± 1.74	2.11 ± 1.56	0.56
Initial FEV_1 %/SD	57. 31 ± 13.04	50.37 ± 13.97	0.10

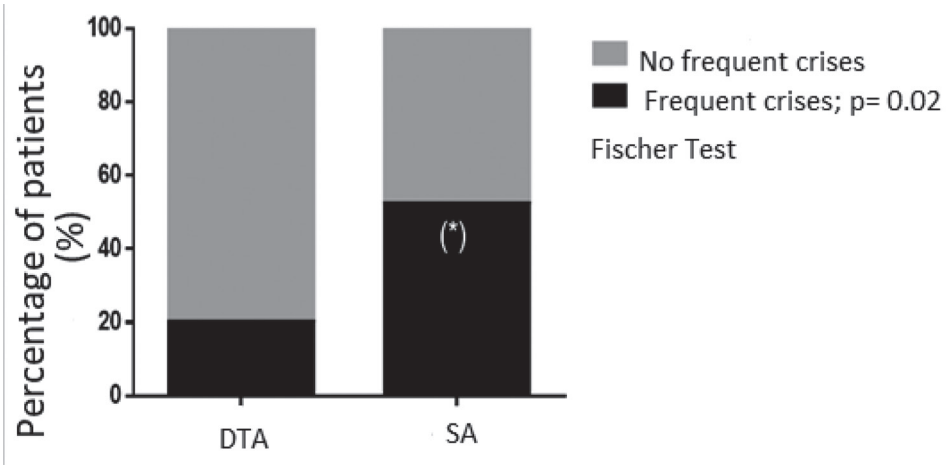
BMI: body mass index; ACT: Asthma Control Test; ACQ: Asthma Control Questionnaire; DTA: difficult-to-treat asthma; SA: severe asthma; SD: standard deviation

and 85% of patients with DTA reported comorbidities; 2 out of the 3 patients without comorbidities were overweight (BMI > 25 kg/m²). The most frequently reported comorbidities in the SA group were: obesity, GERD and OSAHS; and in the DTA group, the most frequent were GERD, obesity and OSAHS. History of psychiatric disorders was more common in patients with SA (**Table 2**).

With regard to the biomarker study, 82% of the patients evaluated in this study showed blood eosinophilia ≥ 150/mm³ , 90% in patients with SA and 50% in DTA, with a median of 639 (range between 34 and 1581) eosinophils /mm³ in SA and 271 (range between 53 and 5300) eosinophils/mm³ in DTA, non-significant difference were found. Seventy seven percent of patients had an elevated IgE, 72% SA and 50% DTA, with a median of 233 (range between 9 and 1494) UI/l in SA and 478 (range between 5 and 2229) UI/l in DTA, difference were found. Differential cell count in sputum sample was performed in 19 patients with SA. 1 was eosinophilic, 2 neutrophilic and the rest were paucigranulocitic. In 3 patients with SA we detected IgE specific for Aspergillus, 2 of which met the criteria for fungi-sensitized severe asthma[8].



Graphic 2. Percentage of patients who had had previous hospitalizations from both groups.



Graphic 3. Percentage of patients with frequent crises at the beginning of follow-up.

TABLE 2. Comorbidities

Comorbidities	DTA (n/%)	SA (n/%)	*p*
Rhinosinusitis	4/20	10/50	0.09
Polyps	2/10	6/30	0.20
OSAHS	5/25	11/55	0.10
Obesity	7/35	13/65	0.11
Psychiatric disease	2/10	8/40	<0.05
GERD	5/25	12/60	0.05
Smoking	4/20	10/50	0.09

OSAHS: obstructive sleep apnea-hypopnea syndrome, GERD: gastroesophageal reflux disease, DTA: difficult-to-treat asthma, SA: severe asthma

As for the treatment, the most commonly used combinations of inhaled corticosteroids and bronchodilators in 40 patients were budenoside/formoterol, indicated in 57% of the cases, followed by fluticasone/salmeterol, used in 30% of the cases; and the remaining patients received fluticasone/vilanterol. 9 of the 20 SA patients received treatment with biologicals. They all started with omalizumab; 3 patients changed to mepolizumab due to a lack of response, and only one patient suspended treatment due to a good clinical response. Omalizumab was indicated only in one patient from the DTA group.

Discussion

Difficult -to-treat asthma accounts for approximately 17% of all asthmatic patients, thus representing the highest healthcare cost within the asthma spectrum. Comorbidities in these patients contribute to the existence of a poor control of symptoms, but their exact impact on asthma control is not fully established[9]. In this work we found that comorbidities were common both in severe asthma patients and in patients with difficult-to-treat asthma, mostly in the first group, though the difference wasn't significant. The most commonly found comorbidity in both groups was obesity, which is possibly a factor that contributes to poor asthma control and also to other comorbidities. Obese patients with severe asthma show more exacerbations, worse control of symptoms, greater use of oral steroids and alterations in functional evaluations[10]. There is 60% prevalence of obesity in severe asthmatics[11]. Obese patients belong to a determined phenotype and are most frequently associated with a neutrophilic-type airway inflammatory profile, thus showing a lower response to treatment with steroids[12]. It has also been established that the lack of response could be mediated by a defect in the glucocorticoid receptors and an increase in oxidative stress [13]. Obesity is also a risk factor for developing other comorbidities such as OSAHS and GERD[10], which were very common in both groups. A mild weight loss that would imply 5-10% of the body weight is associated with better control of asthma symptoms[14].

GERD is a risk factor for asthma exacerbation and poor control of symptoms[13,15]. Asthmatic patients have higher risk of developing GERD than the general population, with a prevalence of 17 to 74%[13,16], in turn, patients with GERD have higher risk of having asthma compared to the general population[17]. Asthma is worse in patients with reflux, whether it is caused by a shifting effect in airway hyperresponsiveness or due to the inflammation produced by aspiration[18]. Also the reflux may trigger symptoms of vocal cord dysfunction that can mimic the asthma symptoms[13]. With respect to the treatment of reflux in asthmatics, inconsistent results have been obtained. Some studies showed an improvement in the symptoms, quality of life and exacerbations related to the treatment of this comorbidity; however, other studies weren't able to prove this improvement[19]. Asymptomatic patients are unlikely to be benefited from treatment with antacids[13].

The asthma-OSAHS combination is associated with worse control of respiratory symptoms, use of rescue short-lasting bronchodilators, rate of exacerbations and lower quality of life[20]. With OSAHS, asthma symptoms may increase, and asthma increases the risk of developing OSAHS, regardless of obesity[21]. Chronic rhinosinusitis, an asthma-related comorbidity, increases the risk of suffering OSAHS[22]. Sleep apneas increase the inflammation of the upper airway; and bronchial neutrophilia and high levels of IL-8 have been reported in untreated patients with OSAHS, compared to OSAHS patients who received treatment[23]. In sleep apneas, the C-reactive protein, the TNF-α and cytokines involved in systemic inflammation are elevated, regardless of the BMI, and could play a determined role in the pathogenesis of asthma[24]. Treatment with continuous positive airway pressure (CPAP) in asthmatic patients improves asthma symptoms, reduces the use of bronchodilators, and improves the peak espiratory flow and quality of life[25], and it has even been shown that in the first 7 days of treatment benefits could already be observed[26].

Anxiety and depression are psychiatric disorders found most frequently in asthmatic patients than in the general population[27]. These conditions are associated with lower adherence to treatment, difficulties in follow-up and symptoms distortion. Patients with insomnia, anxiety and depression have 2.4 times more possibilities of having poor control of respiratory symptoms[20]. It is recommended that during asthma follow-up an evaluation by trained psychologists is carried out for the management of these patients[28].

75% of asthmatic patients have symptoms of chronic sinusitis, and the prevalence of this condition evaluated by tomography reaches up to 84% in severe asthma patients[29]. There could be a correlation between the level of inflammation of the upper airways and the bronchi in patients with chronic sinusitis and severe asthma[30]. This comorbidity associated with asthma is manifested with more coughing, expectoration and risk of exacerbations[15]. The presence of chronic rhinosinusitis associated with nasal polyps is typically observed in patients with late onset asthma who may show allergy to aspirin[31].

Asthma is a heterogeneous condition. Asthma´s observable traits (phenotypes), including the clinical characteristics of the disease and its underlying mechanisms (endotypes) are complex and represent a multitude of host-environment interactions. The cytology of the sputum provides evidence of eosinophils, complex neutrophil mixed inflammation as well as few inflammatory cells in some patients (pauci-granulocytics) [32]. The T2-high endotype includes allergic asthma and late onset eosinophilic asthma. Allergic asthma is characterized by an early onset, positive allergy tests (skin or serum) with allergic rhinitis, IgE > 100 IU mL and mild eosinophilia (< 300 μL). Eosinophilic asthma, on the other hand, is characterized by a late onset, negative allergy tests; low IgE, nasal poly-posis and eosinophilia (300 blood eosinophils/mm^3 or > 2% sputum eosinophils)[33]. 70% of evaluated patients with SA had more than 300 eosinophils/mm^3, and most patients were allergic, given that 74% had an elevated IgE. The correct phenotipification of the DTA patient, and specially patients diagnosed with SA would allow a targeted treatment.

Conclusions

The anthropometric characteristics, control of symptoms and FEV1 in patients with SA and DTA were similar. During follow-up, comorbidities were detected frequently in both groups, especially obesity, GERD and sleep apneas, which are interconnected. Though they were more common in the SA group, there weren't any significant differences between both groups. The history of psychiatric diseases was more common in the group of SA. There were significant differences regarding frequent exacerbations, which were stronger in patients with SA.

It isn't easy to classify both groups, and most patients show overlapping characteristics. Comorbidities occur frequently in both groups, and many of them are difficult to treat or need a long time to be resolved or controlled, such as obesity, rhinosinusitis or smoking; however, with the biomarker analysis and clinical history, the swelling agent is still in many cases the main target of these patients' treatment. So, in patients with difficult-to-treat asthma, we should identify the phenotype of the disease, because even with unresolved comorbidities, the progression of the asthma treatment shouldn't be limited, especially in cases of inadequate disease control.

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