Severe asthma: how can we differentiate phenotypes?

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Summary

Difficult-to-treat asthma, severe asthma or refractory asthma are all terms defining a fraction of asthmatics (5–10%) whose asthma cannot be controlled with a combination of high-dose inhaled corticoids together with long-acting β2 agonists. One major step before claiming that a patient has difficult-to-treat asthma is to ensure that asthma is the correct diagnosis. This involves taking a history of symptoms suggestive of asthma together with objective evidence of variable airflow limitation and/or airway hyperresponsiveness, calling for an intensive initial investigation taking in associated comorbid conditions and multiple re-evaluations over a period of at least 6 months.

The pathophysiology of severe/refractory asthma is likely to be different from that of the mild to moderate form. The immune mechanisms underlying the inflammatory process are not purely Th2. The contribution of allergic mechanisms is usually less prominent than in mild to moderate asthma, and other environmental factors such as air pollution, including tobacco smoke and viruses, may be determinant. Involvement of small airways causing air trapping appears to be crucial in making asthma refractory to classic treatment.

Several phenotypes have been identified on the basis of demographic, functional, pathological and clinical characteristics, which may sometimes overlap. A cluster analysis has identified two clusters specific to refractory asthma: an early onset symptom-predominant asthma and a late onset inflammation-predominant form.

Teasing out mechanisms underlying different phenotypes is essential in finding a new treatment target to improve asthma control in these patients.

Key words: asthma; phenotypes; diagnosis

Introduction

Severe asthma has attracted most attention over the last decade and continues to be a challenge for clinicians and scientists. A worldwide phone survey (AIRE study) has revealed that 18% of asthmatics in western Europe should be considered severe according to the GINA 1998 definition, taking into account symptoms and β2-agonist consumption. This figure obviously overestimates the proportion of real severe asthmatics, since many of the patients reporting symptoms and daily β2-agonist consumption in that survey were not regularly taking inhaled corticosteroids [1]. Although estimated to represent 5–10% of all asthmatics, the severe asthma group accounts for up to 40–50% of health care costs due to asthma, owing to frequent hospital admissions, use of emergency services and drug consumption [2].

Definition

Before considering asthma to be severe it is of paramount importance to establish the diagnosis of asthma itself, since confounding diseases may result in misdiagnosis. According to a survey conducted in United Kingdom emergency departments, a substantial proportion of severe refractory asthma patients were found to actually be suffering from bronchiectasis, COPD, anxiety or vocal cord dysfunction, although real asthma may sometimes coexist with these alternative diagnoses [3]. In addition, truly severe asthma is often accompanied by significant comorbidities such as gastrooesophageal reflux, nasal polyps, obesity and depression. The term severe refractory asthma applies to patients who remain difficult to control despite extensive re-evaluation of diagno-
Clinical features.

Refractory asthma definition was established (table 1) [5]. According to this workshop the term refractory asthma implies the presence of at least one major and two minor criteria. Importantly, these criteria focus on the medication needed to achieve the best possible control, and some of them take into account severe events of past history such as an episode of near fatal asthma. In practice it is generally considered that an asthmatic who cannot be controlled by a combination of high doses of inhaled corticoids and long acting β2-agonist is a severe refractory asthmatic. On this view the definition of asthma control for the clinician is obviously crucial and has recently been facilitated by the validation of several questionnaires such as the Juniper ACQ (asthma control questionnaire) or the ACT (asthma control test) recommended by the latest GINA guidelines [6].

An American multicentre severe asthma research programme (SARP) investigating health care resource utilisation found, not surprisingly, that severe asthma defined according to the ATS workshop was associated with increased health care use as compared with mild to moderate asthma. Interestingly, daily or weekly night awakenings were particularly associated with the extreme clinical condition leading to the ICU (intensive care unit), while daily shortness of breath was associated with persistent FEV1 impairment but not with ICU events [7].

### Risk factors

From the European multicentre study EN-FUMOSA it emerged that female gender and female obesity were marked risk factors for severe asthma [8]. By contrast, this study showed that the proportion of atopy demonstrated by positive skin prick test to common aeroallergens was somewhat less than that seen in mild to moderate asthma, although not negligible (55% of cases) [8]. On the other hand, smoking is now recognised as a major factor contributing to severe asthma, by aggravating symptoms and accelerating lung function decline [9]. Further, the oxidative stress generated by cigarette smoke induces corticosteroid resistance at the molecular level by inactivating histone deacetylase 2 (HDAC2) [10]. A recent prospective cohort study from the European Community Respiratory Health Survey (ECRHS) has shown that early FEV1 impairment, high total serum IgE and persistent productive cough in childhood are strong predictors of moderate to severe asthma in adulthood [11].

### Phenotypes

The recent emphasis on the asthma phenotypes is intended to highlight the heterogeneity of the disease. It is categorised on the basis of demographic, functional, pathological and clinical characteristics, which may sometimes overlap. There are currently several recognised clinical phenotypes of severe asthma. These phenotypes are based on age of asthma onset, rate of exacerbation, presence of chronic airflow limitation and resistance to corticosteroids.

Early onset (<12 years) asthma usually has several atopic features such as eczema and rhinitis, and a more frequent clinical response to allergen triggers [12]. Interestingly, those patients with late onset asthma have often persistent high blood eosinophilia and high urinary cysteinyl leukotriene levels. The SARP study has shown that those with late onset asthma showed greater impairment of forced vital capacity (FVC), despite a shorter disease duration suggesting remodelling or uncontrolled inflammation in the distal part of the lung [7]. Of interest also is the fact that late onset severe asthma is associated with frequent sinopulmonary infections [7].

Some severe refractory asthmatics show a clear tendency to develop severe exacerbations. It seems that psychological disorders and nasal polyps are marked risk factors for severe exacerbations [13]. In addition, the SARP and TENOR studies showed that with low baseline FEV1, early age at onset, allergic status and aspirin sensitivity severe asthma was also more prone to exacerbate.

### Table 1

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<th>Major criteria</th>
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<tr>
<td>1. Treatment with continuous or near continuous (&gt;50% of year) oral corticosteroids</td>
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<td>2. Requirement for treatment with high-dose inhaled corticosteroids (&gt;1200 μg/d beclometasone)</td>
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<table>
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<th>Minor criteria</th>
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<tr>
<td>1. Requirement for additional daily treatment with a controller medication (LABA*, LTRA* or theophylline)</td>
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<td>2. Asthma symptoms requiring short-acting β2 agonist use on a daily or near-daily basis</td>
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<td>3. Persistent airway obstruction (&lt;80% pred), diurnal PEF variability &gt;20%</td>
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<td>4. One or more urgent care visits for asthma per year</td>
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<td>5. Three or more oral corticoid “bursts” per year</td>
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<td>6. Prompt deterioration with &lt;25% reduction in oral or inhaled corticoid dose</td>
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<td>7. Near-fatal asthma event in the past</td>
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* LABA: Long-acting β2 agonists, LTRA: Leukotriene receptor antagonists
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An intervention longitudinal study has clearly shown that uncontrolled airway eosinophilic inflammation favours severe exacerbation [15].

Besides the exacerbation-prone phenotype some severe asthma chiefly displays irreversible airflow limitation, albeit only moderately symptomatic [14]. This accelerated lung function decline has been poorly studied over time. However, cross-sectional studies have revealed that this feature was associated with late onset of the disease, severe hyperresponsiveness to methacholine and high sputum eosinophil counts [16]. On the other hand, another study has shown that both the duration of asthma and the irreversible airflow limitation were related to sputum neutrophil counts [17]. Taken together, both studies suggest that fixed airway obstruction is often accompanied by intense persistent granulocytic infiltration of the airways. The presence of eosinophils, however, would suggest that improved control may be achieved by raising the corticoid dose [18], while the neutrophils indicate corticoid-resistant asthma [19]. The predominance of eosinophils or neutrophils in the airways of asthmatics probably depends on the type of environmental stimulus to which the subject is exposed. The granulocyte pattern found in sputum would then reflect the relative influence of several types of environmental factor, as suggested by the proposed concept of multiple hits in severe asthma [20]. When endotoxins or toxic gas exposures are predominant in driving airway inflammation, neutrophils prevail while an eosinophilic pattern reflects sustained allergen exposure. Using a cluster analysis on a large sample of asthmatics recruited from primary and secondary care, Haldar et al. identified five clusters among the asthmatic population. These were 1) benign asthma, 2) early onset atopic asthma, 3) early symptom-predominant asthma, 4) obese non-eosinophilic asthma, and 5) inflammation-predominant asthma. Two of these clusters (early onset atopic and obese non-eosinophilic) were common to both mild to moderate and refractory asthma, while the two clusters characterised by a marked discordance between symptoms and inflammation (early onset symptoms-predominant and late onset inflammation-predominant) were specific to refractory asthma [21].

Pathophysiology of severe asthma

There is evidence that severe asthma features both persistent inflammation and profound remodelling. While possibly related, the two events appear to be largely independent processes. Although antiinflammatory drugs, and corticosteroids in particular, may be effective in curtailing airway inflammation, their action on airway remodelling is much less clear [22]. Among the remodelling features seen in asthma, one particular focus of study has been airway smooth muscle, the mass of which appears to be clearly increased in severe asthma as opposed to mild to moderate asthma or COPD [23]. Thickness of the basement membrane, though of unknown pathophysiological relevance, has been shown to be increased in severe asthma as compared to mild asthma and COPD [24]. In fatal asthma these inflammatory and remodelling processes are found not only in large but also small airways [25]. An interesting study has used exhaled nitric oxide as a marker of airway inflammation. It has shown that alveolar NO but not bronchial NO was increased in refractory asthmatics as compared to mild to moderate asthma [26]. Severe asthmatics, even when in a stable condition with normal FEV1, values, display signs of small airway dysfunction such as raised closing volume [27] or raised slope at the single breath nitrogen washout-test [28]. Interestingly, asthmatics showing a fall in forced vital capacity (FVC) during a methacholine challenge are those prone to develop severe exacerbations [29]. In addition, in the SARP study severe asthma exhibited more prominent air trapping relative to the level of airflow limitation [30]. Indeed, for the same level of FEV1/FVC ratio, patients with severe asthma had a lower FVC and raised RV/TLC ratio as compared to non-severe asthma [30].

Conclusion

The new definition of severe asthma takes into account both clinical status and use of health care resources. Now that a working definition has been accepted, there is no doubt that severe/refractory asthma will be an area of intensive research. What is called severe refractory asthma is likely to be a heterogeneous disease with several distinct phenotypes, as indicated by the clinical and functional pattern as well as the different inflammatory profile visible in the sputum. Teasing out the mechanisms underlying the different phenotypes is essential in finding new targeted strategies to improve the daily life of severe asthmatics.
References


