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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 β_2 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 β_2-agonist consumption. This figure obviously overestimates the proportion of real severe asthmatics, since many of the patients reporting symptoms and daily β_2-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-

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Table 1

Refractory asthma ATS workshop consensus for typical clinical features.

Major criteria
1. Treatment with continuous or near continuous (>50% of year) oral corticosteroids
2. Requirement for treatment with high-dose inhaled corticosteroids (>1200 µg/d beclomethasone)
Minor criteria
1. Requirement for additional daily treatment with a controller medication (LABA*, LTRA* or theophylline)
2. Asthma symptoms requiring short-acting b2 agonist use on a daily or near-daily basis
3. Persistent airway obstruction (<80% pred), diurnal PEF variability >20%)
4. One or more urgent care visits for asthma per year
5. Three or more oral corticoid "bursts" per year
6. Prompt deterioration with <25% reduction in oral or inhaled corticoid dose
7. Near-fatal asthma event in the past

* LABA: Long-acting b2 agonists, LTRA: Leukotriene receptor antagonists

sis and management over an observation period of at least 6 months [4]. An ATS workshop has defined several criteria by which the term refractory asthma can be 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 β_2-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 FEV_1 impairment but not with ICU events [7].

Risk factors

From the European multicentre study ENFUMOSA 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 FEV_1 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 allergic 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 polyposis are marked risk factors for severe exacerbations [13]. In addition, the SARP and TENOR studies showed that with low baseline FEV_1, early age at onset, allergic status and aspirin sensitivity severe asthma was also more prone to exacerbate

[14]. 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 curbing 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 FEV_1 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

1 Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, Weiss ST. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. J Allergy Clin Immunol. 2004;114:40–7.

2 Serra-Batlles J, Plaza V, Morejon E, Comella A, Brugues J. Costs of asthma according to the degree of severity. Eur Respir J. 1998;12:1322–6.

3 Heaney LG, Robinson DS. Severe asthma treatment: need for characterising patients. Lancet 2005;365:974–6.

4 Chanez P, Wenzel SE, Anderson GP, Anto JM, Bel EH, Boulet LP, et al. Severe asthma in adults: what are the important questions? J Allergy Clin Immunol. 2007;119:1337–48.

5 Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. Am J Respir Crit Care Med. 2000;162:2341–51.

6 Global Initiative for Asthma. National Heart and Lung Institute, National Institutes of Health USA, and the World Health Organization. Updated november 2006. Available at: http://www.ginasthma.org. Ref Type: Generic

7 Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol. 2007;119:405–13.

8 The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. Eur Respir J. 2003;22:470–7.

9 Gusbin N, Garzaniti N, Louis R. Asthma and tobacco. Rev Med Liege. 2006;61:81–6.

10 Ahmad T, Barnes PJ, Adcock IM. Overcoming steroid insensitivity in smoking asthmatics. Curr Opin Investig Drugs 2008; 9:470–7.

11 de Marco R, Marcon A, Jarvis D, Accordini S, Almar E, Bugiani M, et al. Prognostic factors of asthma severity: a 9-year international prospective cohort study. J Allergy Clin Immunol. 2006;117:1249–56.

12 Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. J.Allergy Clin.Immunol. 2004;113: 101–8.

13 ten Brinke A, Sterk PJ, Masclee AA, Spinhoven P, Schmidt JT, Zwinderman AH, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respir J. 2005;26:812–8.

14 Wenzel SE. Asthma: defining of the persistent adult phenotypes. Lancet. 2006;368:804–13.

15 Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet. 2002; 360:1715–21.

16 ten Brinke A, Zwinderman AH, Sterk PJ, Rabe KF, Bel EH. Factors associated with persistent airflow limitation in severe asthma. Am J Respir Crit Care Med. 2001;164:744–8.

17 Little SA, MacLeod KJ, Chalmers GW, Love JG, McSharry C, Thomson NC. Association of forced expiratory volume with disease duration and sputum neutrophils in chronic asthma. Am J Med. 2002;112:446–52.

18 ten Brinke A, Zwinderman AH, Sterk PJ, Rabe KF, Bel EH. "Refractory" eosinophilic airway inflammation in severe asthma: effect of parenteral corticosteroids. Am J Respir Crit Care Med. 2004;170:601–5.

19 Louis R, Djukanovic R. Is the neutrophil a worthy target in severe asthma and chronic obstructive pulmonary disease? Clin Exp Allergy. 2006;36:563–7.

20 Pavord ID, Birring SS, Berry M, Green RH, Brightling CE, Wardlaw AJ. Multiple inflammatory hits and the pathogenesis of severe airway disease. Eur Respir J. 2006;27:884–8.

21 Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med. 2008;178:218–24.

22 Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. Lancet. 2006;368:780–93.

23 Benayoun L, Druilhe A, Dombret MC, Aubier M, Pretolani M. Airway structural alterations selectively associated with severe asthma. Am J Respir Crit Care Med. 2003;167:1360–8.

24 Bourdin A, Neveu D, Vachier I, Paganin F, Godard P, Chanez P. Specificity of basement membrane thickening in severe asthma. J Allergy Clin Immunol. 2007;119:1367–74.

25 Carroll N, Elliot J, Morton A, James A. The structure of large and small airways in nonfatal and fatal asthma. Am Rev Respir Dis. 1993;147:405–10.

26 Berry M, Hargadon B, Morgan A, Shelley M, Richter J, Shaw D, et al. Alveolar nitric oxide in adults with asthma: evidence of distal lung inflammation in refractory asthma. Eur Respir J. 2005;25:98–91.

27 in 'tVeen JC, Beekman AJ, Bel EH, Sterk PJ. Recurrent exacerbations in severe asthma are associated with enhanced airway closure during stable episodes. Am J Respir Crit Care Med. 2000;161:1902-1906.

28 Bourdin A, Paganin F, Prefaut C, Kieseler D, Godard P, Chanez P. Nitrogen washout slope in poorly controlled asthma. Allergy. 2006;61:85–9.

29 Gibbons WJ, Sharma A, Lougheed D, Macklem PT. Detection of excessive bronchoconstriction in asthma. Am J Respir Crit Care Med. 1996;153:582–9.

30 Sorkness RL, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Chung KF, et al. Lung function in adults with stable but severe asthma: air trapping and incomplete reversal of obstruction with bronchodilation. J Appl Physiol. 2008;104:394–403.