

Editorial

The many faces of severe asthma

M. Humbert

Service de Pneumologie, Hôpital Antoine-Béclère,
Assistance Publique – Hôpitaux de Paris, Clamart,
France

Marc Humbert, MD, PhD
Service de Pneumologie
Hôpital Antoine Béclère
157 rue de la Porte de Trivaux
92140 Clamart
France

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Severe difficult-to-control asthma represents a small minority of the whole asthmatic population but this subset of the disease has a major impact on the direct and indirect asthma healthcare costs and the overall burden of asthma (1–4). Although most asthmatics can be managed with a combination of anti-inflammatory drugs and bronchodilators, patients who remain symptomatic despite maximum combination treatment represent a complex and heterogeneous group of patients (1, 2). Severe asthma indeed corresponds to different clinical, functional and pathophysiological phenotypes both in adults and in children (1, 2). In the present issue of *Allergy* several original contributions provide novel information on these difficult asthma phenotypes.

Airway remodelling

Severe asthma has greatly benefited from pathological analysis of bronchial biopsies of well-phenotyped subjects (1, 2). Benayoun et al. (5) have shown that increased areas of mucous glands and smooth muscle, a higher number of fibroblasts and an increase in collagen deposition may differentiate the severe from the mild disease in adult patients. In children, bronchial biopsies are more difficult to sample and analysis of these precious specimens may provide important information to our community (6, 7). It is thus of major interest to highlight the novel data by Tillie-Leblond et al. (7) who studied bronchial biopsies from severe asthma with persistent symptoms in two groups of children with or without persistent airflow obstruction. Of note, structural abnormalities of airway remodelling were present in children with severe asthma (7). Only an increase in airway

smooth muscle and the density of the vascular network were more pronounced in children with persistent airway obstruction whereas reticular basement membrane thickening was similar, indicating that early major bronchial remodelling may take place in the bronchus of children with severe asthma (7).

Rhinitis

Asthma and rhinitis are related diseases and retrospective studies provide evidence that rhinitis is associated with more severe asthma (8, 9). Ponte et al. (10) have enrolled and prospectively followed up 557 patients displaying severe asthma to evaluate whether rhinitis was a predictor of increased asthma severity. In logistic regression models, moderate/severe rhinitis was a predictor for any emergency room visit in the follow-up period, as well as for the presence of uncontrolled asthma after 1 year of follow-up and other markers of poor asthma control and outcome (10). In a multivariate linear regression model, severity of rhinitis was positively correlated with a score of asthma severity and inversely correlated to an index of quality of life (10). These important results confirm that moderate-to-severe rhinitis is a strong predictor for increased severity of asthma.

Outdoor air

As stated by Burney et al. (11), reports on air pollution and asthma exacerbations have been inconsistent, although effects of airborne allergens can be spectacular. In this elegant study, 297 asthmatic patients provided

serum samples and were asked to report any acute respiratory events over the coming months (11). The ability of airborne particle to bind to IgE from the patients was compared for particles sampled on the weekend before their reported exacerbation with particle sampled on the weekend 2 weeks before or after (11). Interestingly, exacerbations were associated with a 25% increase in IgE-binding to particles collected on the previous weekend compared with the control weekends. Of note, this increase was not higher in patients with positive skin-test or those sensitized to grass or tree pollens, supporting the concept that airborne allergen may be an important cause of exacerbations even in those with so called intrinsic asthma (11, 12).

Obesity

It is now clear that obesity and asthma are associated disorders (13–15). In a cross-sectional population-based study of 3609 Danish men and women aged between 30 and 60 years, Husemoen et al. (14) showed that obesity was associated with increased risk of aeroallergen sensitization as well as allergic and nonallergic asthma. Insulin resistance was associated with aeroallergen sensitization and allergic asthma, but not nonallergic asthma (14). van Veen et al. (15) have studied 136 nonsmoking asthmatics with persistent symptoms despite high doses of inhaled or oral corticosteroids and long-acting bronchodilators. Obesity in patients with difficult-to-treat asthma was inversely related with sputum eosinophils, exhaled nitric oxide and positively associated with the presence of co-morbid factors (gastro-oesophageal reflux and sleep apnoea) and reduced lung volumes, suggesting that other factors than airway inflammation alone explain the relationship between obesity and asthma severity (15). These findings support a therapeutic approach of obese patients with difficult-to-treat asthma aiming for weight reduction and control of co-morbid factors.

Occupational exposures

Deleterious occupational exposures may favour the occurrence of severe asthma and several studies indicate

that a considerable proportion of patients do not recover from occupational asthma (16). Indeed, respiratory symptoms and nonspecific bronchial hyperresponsiveness have been reported to persist for years in the majority of diisocyanate-induced asthma despite cessation of exposure (16, 17). Piirila et al. (17) have analysed in great details 17 patients displaying diisocyanate-induced asthma and showed that after cessation of occupational exposure and during inhaled corticosteroid medication, the degree of bronchial hyperreactivity decreased but that forced expiratory volume in 1 s progressed, with persistent bronchial inflammation including elevated macrophages counts and production of pro-inflammatory cytokines IL-6, IL-15 and TNF- α .

Novel treatments

The importance of identifying the underlying causative factors and the recent introduction of novel therapeutic approaches emphasize the need for careful phenotyping of patients with severe disease to improve management of the individual patient's needs (18–20). Recent clinical trials have evaluated several biological therapies for the treatment of asthma (18–20). However, only a few have reached clinical trials status, and only one, omalizumab, a monoclonal anti-IgE antibody, has been clinically licensed (18–21). In the present issue of *Allergy*, a *post hoc* analysis was conducted on efficacy results of a large, randomized, double-blind placebo-controlled trial previously reported in our *Journal* (INNOVATE) (21, 22). The INNOVATE study showed that add-on omalizumab reduced exacerbations, emergency room visits and improved quality of life in inadequately controlled, severe persistent allergic asthma (21). As exacerbations are relatively infrequent, this novel *post hoc* analysis aimed at assessing efficacy on day-to-day symptoms, and showed that omalizumab significantly improved day-to-day symptoms and quality of life, as compared to placebo (22).

This month Theme in *Allergy* clearly emphasizes the diversity, complexity and relevance of severe asthma in our daily practice. Further well-designed studies should improve our understanding of the epidemiology, pathophysiology and management of this difficult-to-treat population (23, 24).

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