Severe adult-onset asthma: A distinct phenotype

Marijke Amelink, MD,[a] Jantina C. de Groot, MD,[b] Selma B. de Nijs, MSc,[a] Rene Lutter, PhD,[a] Aeilko H. Zwinderman, PhD,[c] Peter J. Sterk, MD, PhD,[a] Anneke ten Brinke, MD, PhD,[b] and Elisabeth H. Bel, MD, PhD[a] *Amsterdam and Leeuwarden, The Netherlands*

Background: Some patients with adult-onset asthma have severe disease, whereas others have mild transient disease. It is currently unknown whether patients with severe adult-onset asthma represent a distinct clinical phenotype.
Objective: We sought to investigate whether disease severity in patients with adult-onset asthma is associated with specific phenotypic characteristics.
Methods: One hundred seventy-six patients with adult-onset asthma were recruited from 1 academic and 3 nonacademic outpatient clinics. Severe refractory asthma was defined according to international Innovative Medicines Initiative criteria, and mild-to-moderate persistent asthma was defined according to Global Initiative for Asthma criteria. Patients were characterized with respect to clinical, functional, and inflammatory parameters. Unpaired *t* tests and χ^2 tests were used for group comparisons; both univariate and multivariate logistic regression were used to determine factors associated with disease severity.
Results: Apart from the expected high symptom scores, poor quality of life, need for high-intensity treatment, low lung function, and high exacerbation rate, patients with severe adult-onset asthma were more often nonatopic (52% vs 34%, $P = .02$) and had more nasal symptoms and nasal polyposis (54% vs 27%, $P \leq .001$), higher exhaled nitric oxide levels (38 vs 27 ppb, $P = .02$) and blood neutrophil counts (5.3 vs 4.0 10^9/L, $P \leq .001$) and sputum eosinophilia (11.8% vs 0.8%, $P \leq .001$). Multiple logistic regression analysis showed that increased blood neutrophil (odds ratio, 10.9; $P = .002$) and sputum eosinophil (odds ratio, 1.5; $P = .005$) counts were independently associated with severe adult-onset disease.
Conclusion: The majority of patients with severe adult-onset asthma are nonatopic and have persistent eosinophilic airway inflammation. This suggests that severe adult-onset asthma has a distinct underlying mechanism compared with milder disease.
(J Allergy Clin Immunol 2013;132:336-41.)

Key words: *Asthma, adult onset, eosinophilia, sinus disease*

It is now well recognized that asthma is a heterogeneous condition with many different subphenotypes.[1] Supervised and unsupervised cluster analyses in various asthmatic populations have defined several asthma subphenotypes and have revealed that age of asthma onset is an important characteristic to distinguish these subphenotypes.[2-5]

Asthma that starts in childhood has been studied extensively and shown to be a subphenotype that is typically characterized by fully reversible airflow obstruction, T_H2-type airway inflammation, and responsiveness to inhaled corticosteroids.[1,6] Asthma that starts in adulthood has received less attention but appears to differ from childhood-onset asthma in many respects.[7,8] Apart from a large variety in trigger factors associated with asthma onset, including respiratory tract infections,[9] molds,[10] cigarette smoke,[11] occupational exposure,[12] and environmental pollutants,[13] there is also a large variability in type of airway inflammation,[1] natural course of the disease,[14] and disease severity.[14] Many patients with adult-onset asthma have mild transient disease,[14] whereas others exhibit a progressive course with frequent severe exacerbations and rapid loss of lung function.[15,16]

To our knowledge, thus far, the clinical and inflammatory characteristics that distinguish patients with severe adult-onset asthma from those with milder forms of the disease have not been studied. This distinction is important because it might provide new clues for the pathophysiology and early detection of the severe late asthma phenotype, which might improve disease outcomes through early and targeted intervention.[17]

The aim of the present study was to investigate whether disease severity is associated with specific phenotypic (clinical, functional, and inflammatory) characteristics among a population with adult-onset asthma. To that end, we first selected patients with severe adult-onset asthma diagnosed according to stringent international criteria[18] and compared their characteristics with those of patients with nonsevere adult-onset asthma. Second, we identified factors that were significantly associated with disease severity.

METHODS

Subjects

Adult patients (age, 20-75 years) with a physician's diagnosis of asthma who visited the pulmonary outpatient clinics of 1 academic and 3 nonacademic hospitals were consecutively screened for possible participation in the study. Patients with nonrelated major comorbidities (eg, emphysema,

From [a]the Department of Respiratory Medicine, Academic Medical Centre, University of Amsterdam; [b]the Department of Respiratory Medicine, Medical Centre Leeuwarden; and [c]the Department of Clinical Epidemiology, Bioinformatics and Biostatistics, Academic Medical Centre, Amsterdam.

Supported by the Dutch Asthma Foundation (3.2.08.027).

Disclosure of potential conflict of interest: M. Amelink has received an unrestricted grant from Novartis. J. C. de Groot has received an unrestricted grant from GlaxoSmithKline. S. B. de Nijs has received an unrestricted grant from GlaxoSmithKline. P. J. Sterk has been supported by one or more grants from GlaxoSmithKline and has received a public-private grant from the Innovative Medicines Initiative by the European Union and the European Federation of Pharmaceutical Industries and Associations. A. ten Brinkel is a member of the Dutch Research Advisory Board of Novartis, has received an unrestricted research grant from GlaxoSmithKline, and has received payments for lectures on severe asthma from GlaxoSmithKline and Boehringer Ingelheim. E. H. Bel is a Board member for Novartis; has consultancy arrangements with Merck and Schering-Plough; has received one or more grants from or has one or more grants pending with EFPIA, Novartis, and GlaxoSmithKline; and has received one or more payments for lecturing from or is on the speakers' bureau for Nicomed, GlaxoSmithKline, and Novartis. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication January 9, 2013; revised April 29, 2013; accepted for publication April 29, 2013.

Available online June 24, 2013.

Corresponding author: Marijke Amelink, MD, Department of Respiratory Medicine, F5-260, Academic Medical Centre, University of Amsterdam, PO Box 22700, Amsterdam NL-1100 DE, The Netherlands. E-mail: M.Amelink@amc.nl.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2013.04.052

Abbreviations used
BMI: Body mass index
FENO: Fraction of exhaled nitric oxide
OR: Odds ratio

sarcoidosis, congestive heart failure, and anemia) and pregnancy were excluded. Current smoking and exsmoking (>10 pack years) were allowed if the patient had at least 12% improvement in FEV_1 percent predicted values after inhalation of 400 μg of salbutamol, as well as a normal diffusion capacity (transfer coefficient expressing carbon monoxide diffusing capacity >90% of predicted value).[19] Of 832 screened patients, 306 had adult-onset asthma (asthma starting at >18 years) according to their medical records. Of these 306 patients, 106 were excluded for the following reasons: a history suggestive of childhood asthma (dyspnea attacks, either spontaneous or during exercise; "bronchitis"; or use of asthma medication during childhood), lack of a firm diagnosis of asthma (ie, documented reversibility in FEV_1 of ≥12% of the predicted value or hyperresponsiveness to inhaled methacholine chloride [PC_{20} <8.0 mg/mL] in the past 5 years), or refusal to participate in the study. All patients had to have stable disease for at least 4 weeks before entering the study.

Severe asthma was defined according to international Innovative Medicines Initiative consensus criteria,[18] whereas mild-to-moderate persistent asthma was defined according to Global Initiative for Asthma 2006 guidelines.[20] Thus 78 patients with severe asthma and 98 patients with mild-to-moderate asthma were included. Twenty-four patients did not fall in either category of asthma severity and were excluded from analysis. Patients with severe asthma were all symptomatic (Asthma Control Questionnaire >1.5) or had experienced at least 2 exacerbations in the past 12 months, despite regular treatment with high-dose inhaled corticosteroids (>1000 μg/d fluticasone equivalent) and a second controller medication. The symptoms of all patients with mild-to-moderate persistent asthma were well controlled with a prebronchodilator FEV_1 of greater than 80% when treated with inhaled corticosteroids, or the patients had mild persistent symptoms (Asthma Control Questionnaire >1.5) with a prebronchodilator FEV_1 of greater than 60% when treated with a maximal 500 μg/d fluticasone equivalent. The present study was approved by the hospital Medical Ethics Board (MEC 08/358; NTR no. 1838), and all patients provided written informed consent.

Study design

In this cross-sectional multicenter study all patients were fully assessed during 1 visit, with the exception of a methacholine challenge test, which was performed during a second visit within 30 days. However, this test could not be performed in 80% of the patients with severe disease, either because of safety reasons or because international standards could not be met.[21] Therefore methacholine challenge tests were not interpreted in the present study.

Patients filled out questionnaires that assessed demographic data, medical history, and medication use, as well as the Asthma Control Questionnaire,[22] the Asthma Quality of Life Questionnaire,[23] and the 22-item Sino-Nasal Outcome Test.[24] Physiologic testing of lung function included prebronchodilator and postbronchodilator spirometry, carbon monoxide diffusion capacity measurement, body plethysmography, and, if possible, measurement of bronchial hyperresponsiveness to methacholine.[21,25-27] Atopic status was assessed based on specific and total IgE levels to a panel of common aeroallergens and food allergens (house dust mite, grass and birch pollen, herbs, molds, cat and dog dander, milk, soy, cod, peanut, ovalbumin, and wheat) by means of ImmunoCAP (Phadia, Uppsala, Sweden). Atopy was defined as a score of greater than 0.35 kU/L for at least 1 of the specific IgEs. Inflammatory status was assessed based on exhaled nitric oxide levels[28] and assessment of blood neutrophils, blood eosinophils, and induced sputum cell differentials.[29,30]

Variables

Age of asthma onset was defined as the age at which a physician had diagnosed asthma for the first time, and asthma duration was calculated as the number of years since diagnosis. One pack year of cigarette smoking was defined as smoking 20 cigarettes a day for 1 year. Patients had a positive history of nasal polyposis if it was diagnosed by an ear, nose, and throat specialist and treated accordingly. Chronic use of oral corticosteroids was defined as the daily use of oral corticosteroids in the previous 3 months. The number of exacerbations was defined as the amount of prednisone bursts needed to control increased asthma symptoms in the past 12 months. Lastly, to allow inclusion of (ex)smoking asthmatic patients and asthmatic patients with "fixed" airflow limitation, we only excluded patients with a smoking history of greater than 10 pack years with persistent airflow obstruction (FEV_1/forced vital capacity ratio <0.7) and less than 12% improvement in FEV_1 after 400 μg of inhaled salbutamol at the time of exclusion.[31]

Statistical analysis

Nonnormally distributed data were log transformed before initial analysis. For comparison between groups, χ^2 tests were used for proportions, and unpaired *t* tests were used for normally distributed variables. Factors associated with severe asthma were assessed by using univariate and multivariate logistic regression analyses, with age, sex, and asthma duration as covariates. All analyses were performed with SPSS version 20.0 (SPSS, Chicago, Ill) or GraphPad Prism 5.0 (GraphPad Software, San Diego, Calif) software. *P* values of less than .05 were considered statistically significant.

RESULTS

One hundred seventy-six patients with adult-onset asthma who met the inclusion and exclusion criteria participated in the study. More than half of the patients with severe asthma (59%) used oral corticosteroids on a daily basis, and 11.5% were receiving anti-IgE treatment.

Differences between patients with severe and mild-to-moderate asthma

As expected, patients with severe asthma consulted their treating physicians more often, made more visits to the emergency department, were more often hospitalized, and were more often admitted to the intensive care unit than patients with mild-to-moderate asthma (Table I).

Demographic characteristics, smoking, atopy, and comorbidities. Compared with patients with milder disease, patients with severe adult-onset asthma did not differ with respect to age, age of asthma onset, or asthma duration. Also, the female/male ratio was not different between patients with severe and those with mild-to-moderate asthma. However, patients with severe adult-onset asthma were less often sensitized to common allergens (52% vs 34%), had more nasal symptoms (higher 22-item Sino-Nasal Outcome Test scores), and had more often a history of nasal polyposis (54% vs 27%, Table II and Fig 1).

Pulmonary function. Postbronchodilator FEV_1 values and postbronchodilator FEV_1/forced vital capacity ratios were lower in patients with severe adult-onset asthma than in those with mild-to-moderate asthma (82.4% vs 97.3% and 80.4% vs 93.5%, respectively). Postbronchodilator residual volume/total lung capacity ratio was higher in patients with severe asthma (98.6% vs 88.1%), which is suggestive of relatively more air trapping (Table III).

Inflammatory markers. Patients with severe asthma showed more evidence of systemic inflammation given the higher levels of blood eosinophils compared with those seen in patients with milder disease (Table IV). With respect to markers of airway inflammation, patients with severe asthma had higher levels of sputum eosinophilia compared with those with mild-to-moderate asthma (median, 11.6% vs 0.8%, respectively; $P = < .001$;