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Effects of older age and age of asthma onset on clinical and inflammatory variables in severe refractory asthma

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ABSTRACT

Background: Asthma in the elderly as well as asthma of adult-onset has been associated with increased morbidity, but little is known specifically about the effects of age on clinical and inflammatory outcomes in severe refractory asthma. The aims of the study were to examine the effects of age [<65 versus ≥65 years] and age of onset of asthma [childhood-onset, <18 versus adult-onset, ≥18 years] on clinical and inflammatory variables in patients with severe asthma.

Methods: In 1042 subjects with refractory asthma recruited to the British Thoracic Society Severe Asthma Registry, we compared patient demographics, disease characteristics and biomarkers of inflammation in patients aged <65 years (n = 896) versus ≥65 years (n = 146) and onset at age <18 years (n = 430) versus ≥18 years (n = 526).

Results: Severe asthma patients aged ≥65 years had improved symptom control, better asthma quality of life and in the last year, less emergency visits and rescue oral steroid courses [3 (1–6) versus 5 (2–7), p < 0.001] than severe asthmatics aged <65 years. Blood eosinophils were lower in the elderly group. Patients with severe adult-onset asthma had similar symptom control, lung function and health-care utilization compared to severe childhood-onset asthma. Adult-onset asthmatics had higher blood eosinophils and were less atopic.

Conclusions: Patients with severe refractory asthma aged ≥65 years exhibit better clinical and health care outcomes and have lower blood eosinophils compared to those aged <65 years. Severe refractory

Abbreviations: ACQ, Asthma control questionnaire; AQLQ, Asthma quality of life questionnaire; ATS, American Thoracic Society; BMI, Body mass index; BTS, British Thoracic Society; CAP, IgE antibody enzyme-immunoassay; ERS, European Respiratory Society; EuroQoL, European Quality of Life; FE_{NO50}, Fraction of expired nitric oxide 50 ml/s; FEV_1, Forced expiratory volume in one second; FVC, forced vital capacity; GORD, gastro-oesophageal reflux disease; HAD, Hospital Anxiety and Depression; ICS, Inhaled corticosteroid; IL, Interleukin; ITU, Intensive Therapy Unit; Kco, Transfer coefficient of the lung; LABA, Long-acting beta$_2$-agonist; RV, Residual volume; SABA, Short acting beta$_2$-agonist; SARP, American Severe Asthma Research Programme; TLC, Total lung capacity; VAS, Visual analogue scale.

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adult-onset asthma is associated with similar levels of asthma control, higher blood eosinophils and less atopy than severe refractory childhood-onset asthma.

1. Introduction

Severe refractory asthma affects all age-groups [1–3]. The prevalence of asthma in the elderly ranges from 7% to 11% [4–6], and with the expected increase in the proportion of elderly people in the population worldwide [4,5,7], understanding the phenotype of asthma in the elderly will be of great importance. Asthma in older people is believed to be under-diagnosed, under-treated and often associated with worse health care outcomes [5,8–11]. Co-morbid conditions, the psychosocial effects of ageing and reduced perception of bronchoconstriction [12] as well as altered airway inflammation [8,13,14] may contribute to worse clinical outcomes in elderly asthmatics [8,9].

To date however, there is limited information on clinical and physiological outcomes and immunological biomarkers of inflammation in older people (aged ≥ 65 years) with severe refractory asthma compared with younger patients (aged < 65 years) with severe disease [15]. In patients recruited to the American Severe Asthma Research Programme (SARP) the probability of severe disease increased with each year of life until the age of 45 years and thereafter increased at a slower rate [16]. Clinical research trials, especially phase 2 studies, frequently exclude subjects aged >65 years [14]. It is important to know whether clinical and inflammatory variables in this group differ from younger patients when utilising new therapies for severe asthma.

Age of asthma onset within the general adult asthma population can affect clinical and inflammatory variables [17,18]. Early-onset adult asthma is associated with poor symptom control and atopy [18,19], whereas adult-onset asthma is associated with female gender, current smoking and greater airflow obstruction [18]. Severe adult-onset asthma may be a distinct phenotype compared to milder forms of adult-onset asthma [20] as it is associated with a greater proportion of non-atopics, worse nasal symptoms, and higher levels of inflammatory biomarkers such as exhaled nitric oxide, blood neutrophils and sputum eosinophils [20]. Adults with early-onset severe asthma have more allergic symptoms, greater allergen sensitivity and less lung eosinophilia than people with severe late-onset asthma [21]. A systematic review of four studies of adults with severe early-onset and late-onset asthma, with sample sizes ranging from 74 to 275 subjects, identified few phenotypic differences due to age of onset [18].

The British Thoracic Society (BTS) Difficult Asthma Network developed a National Registry for dedicated UK Difficult Asthma Services [3]. We analysed this Registry population to examine the effects of age [<65 versus ≥65 years] and age of onset of asthma [childhood-onset, <18 versus adult-onset, ≥18 years] on clinical and inflammatory variables in 1042 patients with severe refractory asthma.

2. Methods

2.1. Study design

All subjects with refractory asthma ≥18 years old from the BTS Severe Asthma Registry were included in the analysis. The definition of refractory asthma was based on the American Thoracic Society (ATS) Criteria [22] and International European Respiratory Society (ERS)/ATS guidelines on definition, evaluation and treatment of severe asthma [23]. The Registry included seven specialised asthma centres in the United Kingdom using established, dedicated assessment protocols, to ensure identification of patients with well-characterised refractory asthma and data was collected at the time of referral to the centre. Subjects provide fully informed written consent for their data to be held in the registry. The Northern Ireland Research Ethics Committee approved research analysis of the data. To analyse the effects of age, the cohort was divided into those ≥65 years and compared with those <65 years of age. For effects of age of onset of asthma, the cohort was divided into childhood-onset of asthma, if asthma symptoms started before the age of 18 years and adult-onset, if symptoms of asthma occurred from the age of 18 onwards [20].

2.2. Assessments

As described previously [3], patients at all centres undergo a systematic assessment, which includes a medical history, asthma-specific questionnaires (Asthma Control Questionnaire [ACQ] scores [24]; Asthma Quality of Life Questionnaire [AQLQ] scores [25]); European Quality of Life [EuroQoL] health scale; and Hospital Anxiety and Depression [HAD] scores. Measurements include spirometry, static lung volumes, transfer coefficient [KCO], induced sputum cell counts, fraction of expired nitric oxide (50 ml/s [FE_{NO50}]); atopy assessment (skin prick tests, serum IgE antibody assays); blood eosinophil counts; serum total IgE concentrations and dual-energy X-ray absorptiometry [DXA] scans. The tests were not performed using identical equipment across the sites because these data were collected from hospital outpatient clinics and not in the setting of a research trial. Atopy was defined as any positive immediate, 15-min, skin prick test wheal response of 3 mm larger than that elicited by the negative control or an *in vitro* IgE antibody serologic test (ImmunoCAP test or equivalent [>0.35 kU/L]) to common inhalant allergens.

2.3. Statistical analysis

Data were analysed using statistical software (Minitab Ltd., Coventry, UK and Med Calc) and continuous variables were summarised as mean [standard deviation] or median (inter-quartile range) depending on Gaussian or skewed distribution respectively. Their comparison, between different age categories, was by Student's *t*-test and Mann-Whitney *U*-tests. Categorical variables were summarised by their observed frequencies and percent within the participant subsets, and were compared using χ^2 test. Age-dependent co-variates and associated p-values were determined using one-way analysis of variance (ANOVA) between patients with <65 and ≥65 years of age (MedCalc v13.2.0, Ostend, Belgium). All analyses were considered descriptive or exploratory therefore a p-value less than 5% was considered significant.

3. Results

1042 subjects with refractory asthma entered in the BTS Severe Asthma Registry were included in the analyses (Table E1, Online Supplement). Age was normally distributed [mean (SD) 49.3 (14.1)