

EDITORIAL

Clinical & Experimental Allergy

Staphylococcal enterotoxin-specific IgE: a biomarker for a distinct phenotype of severe asthma?

This editorial discusses the findings of the paper in this issue by W.-J. Song et al. [1], pp. 411–421.

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In this issue of *Clinical Experimental Allergy*, in a case–control study of 249 patients with asthma aged 65 years or above from nine referral hospitals in Korea, an association between *Staphylococcus aureus* enterotoxin sensitization measured by increased levels of specific IgE to staphylococcal enterotoxin (SE-IgE) and late-onset asthma is reported [1]. This cohort was well characterized as to the presence of asthma, its severity, the degree of airflow obstruction, frequency of exacerbations, the presence of comorbidities, measurement of inflammatory biomarkers including blood and sputum eosinophil counts, and the presence of atopy. Severe asthma was defined according to recent ERS/ATS guidelines [2] and assessed after a 12-month follow-up period. The presence of high levels of SE-IgE was associated with having more severe asthma, more sputum eosinophilia, more chronic rhino-sinusitis and more gastro-oesophageal reflux disease compared to those with lower SE-IgE levels. The significant association of severe asthma with serum SE-IgE was independent of co-variables. Severe asthma was characterized by more frequent exacerbations and systemic corticosteroid rescue therapy, two features that usually track with each other. Thus, this report supports the growing concept that elevated levels of SE-IgE represent a biomarker for a distinct phenotype of severe asthma in elderly patients with late-onset asthma associated with a higher level of chronic rhinosinusitis (associated with or

without nasal polyps), high levels of blood and sputum eosinophilia and serum total IgE.

This study is a further confirmation of two European-based studies that have linked the increased risk of high SE-IgE serum with not only asthma but also with severe asthma [3, 4]. Kowalski et al. [4] reported a threefold higher level of serum SE-IgE in patients with severe asthma recruited in Poland when compared to patients with non-severe asthma and 80% of the patients with severe asthma had high levels of SE-IgE. This cohort had a high prevalence of aspirin hypersensitivity which was more common in the severe asthmatics, and all patients with aspirin hypersensitivity were positive for SE-IgE. Bachert et al. [3] also reported an increased risk for SE-IgE-positive patients to have any asthma (odds ratio of 7.25) or severe asthma (11.09) versus SE-IgE-negative subjects. There was greater use of oral corticosteroids and hospitalization in the SE-IgE high group. In both studies, there was an association between levels of SE-IgE and airflow obstruction as measured by FEV₁, which was not reported in the Korean study [1] where high SE-IgE group had only a mild degree of reduction in baseline FEV₁ compared to the negative SE-IgE group.

The other difference between the European and the Korean cohorts is the reporting of a higher prevalence of chronic rhinosinusitis in the elderly Korean asthmatics with high levels of SE-IgE, which was not reported in the European studies. The study of Kowalski et al. [4] found that the presence of SE-IgE in severe asthma was independent of the presence of nasal polyps. It is unclear whether this is due to differences in the type or background of patients studied. A recent European cohort of severe asthma recruited within UBIOPRED reported high levels of associated allergic rhinitis in both severe and non-severe asthma but with a much higher prevalence of nasal polyps in severe asthma (34%) compared to non-severe asthma (9%), associated with higher nasal symptom scores as

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assessed by the Sino-Nasal Outcome Test (SNOT-20) Questionnaire [5]. The Korean study [1] had patients ≥ 65 years old while the severe asthma participants in Bachert et al. study [3] were younger with a mean age of 46.5 years. Thus, age could be a predominant factor in determining that high levels of SE-IgE are indicative of a greater risk for severe asthma associated with chronic rhinosinusitis.

The relationship of SE-IgE positivity with atopy defined by positive skin prick test to 55 common inhalant aeroallergens has also been elucidated in the study of Song et al. [1]. Those with high levels of SE-IgE were associated with higher levels of total serum IgE, but the presence of atopy was not associated with severe asthma in agreement with the European studies [3, 4]. A total of 33.5% of late-onset elderly patients with asthma had high levels of SE-IgE, while 27.9% in the non-atopic groups also had high levels. The prevalence in the non-atopic group is of special interest as this group would be considered non-atopic, and yet 28% will have shown evidence for sensitization to SE and express Th2 high cytokines, a very similar proportion reported in the Bachert et al. [3] study (21%).

While there is strong evidence that SE-IgE could be a marker of severe asthma, what about the potential involvement of Staphylococcus enterotoxins (SE) particularly enterotoxin B (SEB) in the pathophysiology of severe asthma? SE are superantigens that can activate T cells to cause polyclonal activation of T cells in nasal and airway tissues and also other inflammatory cells such as B cells, eosinophils and epithelial cells [6]. In human nasal mucosa, SEB induces the release of Th2 cytokines, IL-4, IL-5 and IL-13, which would contribute to the persistence of Th2 inflammation [7]. In addition, SEB induces IgE antibody production by activating B cells [8, 9], as has been shown in nasal polyp tissues [10]. The contribution of the polyclonal IgE formed locally to disease severity is not clear. Stimulation of nasal mucosal tissues with common aeroallergens such as house dust mite or grass pollen or with SEB caused mast cell activation dependent on the presence of local IgE antibodies, but independent of systemic IgE antibodies [11]. Much less is known about the potential

effects of SEB in the lower airways, although it is known that *Staphylococcus aureus* measured as 16S rRNA is increased in the lower airways of asthmatic children in particular [12]. However, in relation to severe asthma, T cell activation induced by SEB is reported to be corticosteroid resistant [13] and SEB increases airway inflammation caused by allergen exposure in sensitized animals [14, 15]. These available data on the actions of SEB would support a plausible role for SEB in underlying the pathophysiology of severe asthma. Furthermore, work derived from an analysis of nasal polyp tissue has indicated that in patients with nasal polyps, the expression of IL-5 and SE-IgE in the polyps indicated the presence of asthma as a comorbidity [16].

The SE-IgE endotype of severe asthma might be responsive to anti-IgE therapy with omalizumab. Although anti-IgE therapy with omalizumab is currently reserved for atopic severe asthma, there are increasing reports of patients with non-atopic asthma responding to treatment with omalizumab [17, 18]. As noted above, some of these responders could represent non-atopic asthmatics with high levels of circulating SE-IgE. In a recent study, patients with severe nasal polyps and asthma demonstrated a beneficial response in terms of both upper and lower airway symptoms with clinical efficacy in controlling both nasal polyps and asthma irrespective of their atopic status [19]. This needs to be confirmed in larger studies. Another possibility is that the presence of high SE-IgE serum levels could be a biomarker of therapeutic response with anti-IL5 antibody treatments; recent studies with this treatment have used blood eosinophil counts in the range of 150–300/ μ L as stratification in patients with severe asthma to Phase 2 studies of this therapy [20]. Accepting the premise that SE may be driving this phenotype of late-onset severe asthma associated with chronic rhinosinusitis and nasal polyps and sputum eosinophilia leading to raised SE-IgE and eosinophilic asthma will lead to new avenues of treatment for severe asthma.

Conflict of interest

The authors declare no conflict of interest.

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