Relationship between IgE sensitisation to Staphylococcus aureus enterotoxin B, asthma severity and atopy

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Super-antigenic properties of *Staphylococcus aureus* enterotoxins (SE) considered as a whole [Staphylococcus aureus enterotoxins C (SEC), A (SEA), B (SEB), and toxic shock syndrome toxin (TSST-1)] have been associated with atopic dermatitis [1], chronic rhinosinusitis [2,3] and asthma [2,4]. The presence of serumspecific IgE(sIgE) againsta mixture of SE (SE-sIgE) has been suggested as an important risk factor for severe asthma in adult asthma patients with poor lung function and eosinophilia [5-7]. However, there are few studies that analyse each SE individually. In particular, the presence of sIgE to SEB (SEB-sIgE) has been associated with severe atopic dermatitis [8] but there is still little evidence of an association between SEB-sIgE and asthma [9,10].

The aim of this study was to determine whether the presence of SEB-sIgE is associated with asthma severity,level of control and atopy in an asthmatic population.

A retrospective observational study was conducted among patients ≥ 18 years oldwith a diagnosis of asthma in the severe asthma unit at La Paz University Hospital in Madrid, between 2009 and 2013. Sensitization was defined as SEB-sIgE≥ 0.35 KU/L. The Hospital's Clinical Research Ethics Committee approved the study protocol (PI-2986).

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Patients were classified based on asthma severity as per the Spanish Guide for the Management of Asthma (GEMA) [11]. Uncontrolled patients were those who suffered exacerbations requiring oral steroids for at least three consecutive days or hospital admission in the year prior to the study [12].

Atopy was determined based on the results obtained with skin prick-testand/orsIgEto common aeroallergens: pollens*(Cupressusarizonica, Platanusacerifolia, Oleaeuropaea, Loliumperenne, Artemisia vulgaris, Salsola kali, Parietariajudaica*), house dust mites*(D. pteronyssinus, D. farinae*), animal dander(dog, cat) and molds*(Aspergillus fumigatus, Alternariaalternata, Cladosporiumherbarum, Candida albicans*).Skin prick-test results were considered positive when a wheal diameter ≥ 3 mm was obtained in comparison with the negative (normal saline) control, in the presence of a positive (10 mg/mL histamine)control [13]. A value of sIgE ≥0.35 kU/L was consideredpositive. The statistical analysis was completeusing the R Stats software.

A number of 266 asthmatic patients were included, 75.2% women (Table I).Average age was 48.42 years (18-83 years); 44 patients (16.5%) with positive SEB-sIgE, and sixof them (13.6%) weremonosensitized to SEB-sIgE.

The average value of SEB-sIgE was 2.15 kU/L (0.36-4.50 kU/L); 237 patients (89.1%) had uncontrolled asthma and 101 (38%) had severe asthma, 67 of these required regular treatment with oral corticosteroids (66.3%).

Asthmatic patients with positive SEB-sIgE were younger and with a more homogeneous gender distribution, their asthma was better controlled, and they had more atopic

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dermatitis, higher total IgE levels, more sensitisations to aeroallergens, more eosinophils in peripheral blood and higher levels of FeNO (fractional exhaled nitric oxide) than patients with negative SEB-sIgE. No significant differences were found between the different levels of severity or lung function and the presence of SEB-sIgE.The analyses were repeated to rule out dependence on atopic dermatitis (35 patients with atopic dermatitis were excluded),and significant differences remained with regard to age (p=0.019), sex (p=0.004), total IgE (p=0.000) and sensitization to hose dust mites (p=0.013) and fungi (p=0.013). The number of eosinophils tended to be significant (p=0.057).

We found a prevalence of SEB-IgE sensitisation of 16.5% in our asthmatic population, which is closer to Tanaka et al [9] (22.15%) than to Matsumoto et al [10] (42%). These differences may be due to the fact thatdiverse populations were studied with different methodologies. In our study, about 70% were moderate-severe asthmatics and 89% haduncontrolled asthma. In the Matsumato et al [10] study less than 20% were at GINA step 5 and 25% were poorly controlled. In Tanaka's study [9], the patients were more evenly distributed among the severity stages and 13% were uncontrolled. Matsumoto et al [10] chose a SEB-sIgEcut-off for positivity of ≥0.1 kU/L. Like Tanaka et al [9], we considered the same cut-off criterion (≥0.35 kU/L) for both SEB and aeroallergens.

The results in terms of association with asthma control are mixed. Matsumoto et al [10] found that both SEA-sIgEand SEB-sIgE (plus SEA-sIgE) were associated with poorer asthma control. Conversely, Tanaka et al [9], like us, did not find the presence of SEB-sIgE to be associated with poorer asthma control (they only found this association with SEA-IgEs).

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Again like Tanaka et al [9], we did not find an association between SEB-IgEs and inflammatorybiomarkers (eosinophils in peripheral blood and FeNO) or lung function when corrected for atopic dermatitis. Unlike other authors[2,3,5-7], we did not find an association with the presence of chronic rhinosinusitis, which could be due to the aforementioned reasons and that we have not used a mixture of SE. It would have been interesting to study the patientsmonosensitisedto SEB in our population to confirm the results obtained;however, the sample size was too small.

The clinical differences found between patients with SEA and SEB sensitisation are probably due to the fact that there is only 31% homology in their amino acid sequences and their mechanisms of binding to MHC Class II molecules are different; SEA is Zn++ dependent and SEB is metal independent [9]. This means that the immune behaviour of each of the SEs needs to be studied and evaluated individually.

In our asthmatic patients, SEB sensitisation was associated with the presence of atopic dermatitis and with an increased risk of sensitisation to common aeroallergens. Sørensen et al [14] found similar results in a cross-sectional study in adolescents (with SEA, SEB, SEC, and TSST), although their cut-off point for SE-sIgE was >0.1 kU/L. They concluded that sensitisation to SEs was associated with polysensitisation to food and inhalant allergens as well as with allergic multi-morbidity, supporting the mechanism by which *S. aureus* antigens act as T-cell dependent superantigens causing B cell polysensitisation [15]. Another finding that supports this theory is that most authors [2,5,6,7,9,10], like us, found a stronger association between elevated total IgE levels and SE-sIgE.

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Finally, as we are in the age of Precision Medicine, it is important to underline that sensitization to each enterotoxin should be assessedindividually, and that the presence of atopic dermatitis should be taken into account, as this could affect the results obtained. Moreover, it is necessary to establish unanimously accepted cut-off points for positive SE-sIgEdeterminations.

Conflict of interest

Dr.Quirce reports personal fees and non-financial support from GSK, AstraZeneca, Sanofi, Novartis, Mundipharma, Teva, Allergy Therapeutics, outside the submitted work.The remaining authors have no conflict of interest to declare.

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Table 1. Clinical characteristics of asthma patients

	Patients (n=222) SEB-sIgE (-)	**Patients (n=44) SEB-sIgE (+)**	***p***
Age years, median (range)	52 (18-83)	34.5(18-71)	*0.0002*
Gender, female n (%)	176(79.28)	24(54.54)	*0.0009*
Smokers, n (%)	25 (11.26)	10 (22.7)	*0.1*
Atopic dermatitis, n (%)	23 (10.36)	12 (27.27)	*0.006*
Allergic rhinitis, n (%)	131 (59)	30 (68.18)	*0.37*
CRSwoP, n (%)	74(33.33)	15 (34.09)	*0.87*
CRSwP, n (%)	61 (27.47)	13 (29.54)	
Mild intermittent asthma, n (%)	15 (6.75)	2 (4.54)	*0.19*
Mild persistent asthma,n (%)	39 (17.56)	11 (25)	
Moderate persistent asthma, n (%)	78 (35.13)	20 (45.45)	
Severe persistent asthma, n (%)	90 (40.54)	11 (25)	
Uncontrolled asthma, n (%)	203 (91.44)	34 (77.27)	*0.035*
FEV_1 %, median	82 (29-140)	83.5 (30.6-135)	*0.68*
FEV_1/FVC % postBD, median	74 (32-110)	72 (28-86)	*0.26*
FeNO ppb, median	33 (3-267)	56.25 (16-180)	*0.03*
Tryptase ng/ml, median	4.4 (0-22.4)	4.55 (0-19.6)	*0.48*
Blood eosinophils/µL, median	290 (0-192)	375 (140-2880)	*0.003*
ECP ng/ml, median	36 (0-180)	52.3 (6.20-200)	*0.08*
Atopy, n (%)	138 (62.16)	34 (77.27)	*0.037*
Total IgEkU/L, median	94.5(2.5-2624)	631.5 (51-17226)	*0.0000*
Sensitization to pollen, n (%)	86 (38.74)	25(56.81)	*0.03*
Sensitization to mites, n (%)	23 (10.36)	13 (29.54)	*0.003*
Sensitization to animal dander, n (%)	59(26.57)	22 (50)	*0.004*
Sensitization to molds, n (%)	43 (19.36)	19 (43.18)	*0.001*

SEB-sIgE: Specific IgE to Staphylococcal enterotoxin B. CRSwoP: Chronic rhinosinusitis without polyposis. CRSwP: Chronic rhinosinusitis withpolyposis. ECP: eosinophilcationicprotein. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity.

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