Asia Pacific allergy

pISSN 2233-8276 · eISSN 2233-8268

Hypothesis & Experience
Original Article

http://dx.doi.org/10.5415/apallergy.2013.3.2.120
Asia Pac Allergy 2013;3:120-126

Staphylococcal enterotoxin specific IgE and asthma: a systematic review and meta-analysis

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Background: Recent literature suggests that Staphylococcal enterotoxin specific IgE may be a risk factor for asthma.

Objective: To investigate the associations between Staphylococcal enterotoxin sensitization and asthma.

Methods: A systematic review and meta-analysis was performed for relevant case-control or population-based studies, published in the peer-reviewed journals until February 2013. Data were extracted on study designs, subjects, definitions and the prevalence of Staphylococcal enterotoxin sensitization.

Results: A total of 683 studies were initially identified, of which 7 studies finally met the inclusion criteria (5 case-control and 2 population-based studies). All the included studies reported higher prevalence of the sensitization in asthmatics than in controls, despite clinical and methodological heterogeneity. In a meta-analysis, the pooled odds ratio of the sensitization for asthma was 2.95 (95% confidence intervals 2.28-3.82).

Conclusion: Staphylococcal enterotoxin sensitization was significantly associated with asthma. The mechanisms of associations warrant further elucidation.

Key words: Asthma; Staphylococcus; Meta-analysis

INTRODUCTION

Now it is accepted that asthma is a heterogeneous disorder [1]. In the past, asthma was mainly associated with inhalant allergen sensitization; however, recently it has been found that various risk factors are involved in the complex pathophysiology of asthma.

Current literature suggests the microbial exposure to play various regulatory roles for asthma [2, 3]. Particularly, *Staphylococcus aureus* (*S. aureus*) is a frequent colonizer in upper airways and skin among healthy individuals [4]. It has unique

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Received: March 19, 2013
Accepted: March 22, 2013

immune modulatory properties by secreting enterotoxins [5]. In this regard, previous studies have elucidated the significant associations between Staphylococcal enterotoxins and allergic diseases such as atopic dermatitis [6] or chronic rhinosinusitis with nasal polyps [7].

However, several recent observations [8, 9] and meta-analyses [10] suggested that Staphylococcal enterotoxin (SE) specific IgE (sIgE) is a potential risk factor for asthma also, but there is still scarce data to address the issue. We present here a systematic review and meta-analysis of currently available literatures to summarize the associations between SE sensitization and asthma.

MATERIALS AND METHODS

Literature search

A systematic literature review was performed on Pubmed and Embase databases to identify peer-reviewed articles reporting the prevalence of SE sensitization in asthmatics and controls, published from January 1960 until February 2013, without language restriction. The search utilized the keywords 'asthma OR wheeze OR wheezing' AND 'Staphylococcal OR Staphylococcus'. Additional articles were manually sought through the reference lists of the retrieved articles. The review process followed the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [11], as presented in Fig. 1. Inclusion criteria were 1) the population-based or case-control studies which compared the prevalence of SE sensitization in asthmatics with non-asthmatic controls. Exclusion criteria were 1) the articles without peer-reviewed full-text (i.e., conference abstracts) and 2) the studies which did not determine the positivity of SE sensitization in a standardized manner.

The literature search and review process was performed by two researchers. In cases of disagreement during the selection of relevant studies, it was resolved by discussion within all the authors. The outcome data extracted were: study design, subjects, region/population, and the definition and prevalence of SE sIgE positivity. If prevalence of SE sIgE positivity was not described, corresponding authors were contacted to obtain the data.

Statistical analyses

A pooled estimate of risk for asthma by SE sIgE positivity was calculated by using the fixed-effect models with Mantel-Haenszel methods. The results were expressed as odds ratio (OR) with 95% confidence intervals (CI). Homogeneity testing was performed using the I^2 test. The analysis was performed using the "metan" command in STATA package (release 12.0; StataCorp., College Station, TX, USA).

RESULTS

Pooled analyses

Of 683 potentially relevant publications identified through the literature search, 659 papers were excluded after reading the abstract and title. Further 17 papers were excluded after reading the full text. Finally, 5 case-control studies and 2 population-based studies from peer-reviewed journals were included (Fig. 1). The summary of seven included studies is described in Tables 1 and 2.

The prevalence of SE sIgE positivity among asthmatics widely varied with study populations, ranging from 14.9% to 79.1%; however, the rates showed trends to increase in older subjects and in more severe asthmatics. In non-asthmatic controls, the rate of SE sensitization also ranged widely, from 3.8% to 41.3%. Collectively, all the included articles consistently showed that SE sensitization is more frequent among asthmatics than controls, irrespective of study populations. In the meta-analysis, the pooled odds ratio (OR) of SE sensitization for asthma was 2.95 (95% confidence interval [CI] 2.28-3.82, Fig. 2).

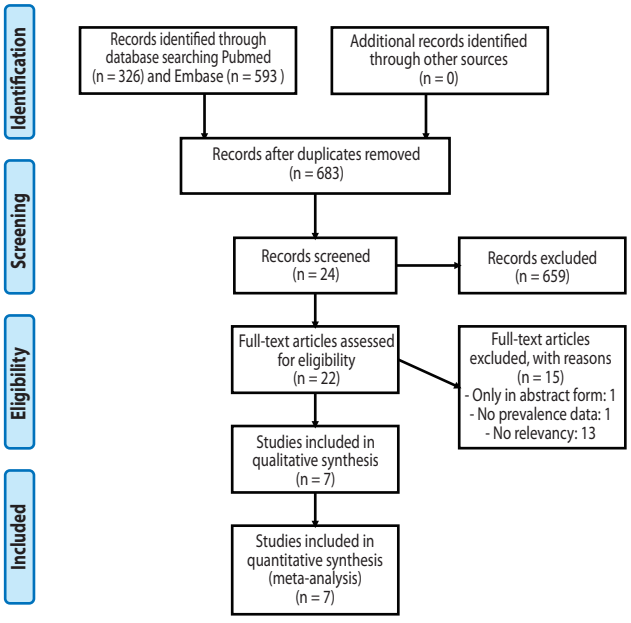

Fig. 1. Flowchart for the identification of relevant studies.

 http://dx.doi.org/10.5415/apallergy.2013.3.2.120

Table 1. Summary of hospital-based case-control studies on the association between Staphylococcal enterotoxin sensitization and asthma

Author [Ref.] (yr)	Subjects	Region	Measures of SE sIgE (Positive cutoff)	SE positivity (%)
Bachert et al. [8] (2012)	Severe asthma = 166; Nonsevere asthma = 152; Control = 69 (mean age 41.3 yr)	UK and Germany	SE mix (SEA, SEC, TSST-1) sIgE (≥ 0.1 kU/L)	59.6% (99/166) in severe asthma 40.8% (62/152) in nonsevere asthma 13.0% (9/69) in controls
Kowalski et al. [9] (2011)	Severe asthma = 109; Nonsevere asthma = 101; Control = 45 (mean age 42.4 yr)	Poland	SE mix (SEA, SEC, TSST-1) sIgE (≥ 0.1 kU/L)	76.1% (79/104) in severe asthma 71.1% (64/90) nonsevere asthma 41.3% (12/29) in controls
Lee et al. [14] (2006)	Aspirin-intolerant asthma = 80; Aspirin-tolerant asthma = 62; Control = 52 (mean age 41.1 yr)	Korea	SEA, SEB, TSST-1 sIgE (≥ 0.35 kU/L)	38.0% (54/142) in asthma 17.1% (7/41) in controls
Lee et al. [15] (2005)	Allergic rhinitis/asthma = 188; Control = 53 (mainly < 20 yr)	Taiwan	SEA, SEB sIgE (≥ 0.35 kU/L)	29.4% (5/17) in asthma 3.8% (2/53) in controls
Rossi and Monasterolo [16] (2004)	Allergic rhinitis and/or asthma = 198; Control = 25 (mean age 22.9 yr)	Italy	SEA, SEB, SEC, SED, TSST-1 sIgE (≥ 0.35 kU/L)	35.5% (22/62) in asthma 4% (1/25) in controls

SE, Staphylococcus aureus enterotoxin; SEA-D, Staphylococcal enterotoxin A-D; TSST-1, toxic shock syndrome toxin-1; sIgE, specific IgE.

Table 2. Summary of population-based studies on the association between Staphylococcal enterotoxin sensitization and asthma

Author [Ref.] (yr)	Subjects	Region	Asthma definition (Prevalence)	Measures of SE sIgE (Cutoff level)	SE positivity (%)
Hollams et al. [12] (2010)	1,380 children (the West Australian Pregnancy Cohort study; aged 14 yr)	Australia	Current asthma; recent symptoms + asthma medication + ever doctor diagnosis (prevalence 10.5%)	SE mix (SEA, SEC, TSST-1) sIgE (≥ 0.35 kU/L)	27.1% (38/140) in asthma; 17.9% (214/1195) in controls
Semic-Jusufagic et al. [13] (2007)	510 children (the Manchester Asthma and Allergy Study; aged 5 yr)	UK	Current wheeze (ISAAC, prevalence 22.1%) Physician-diagnosed asthma (prevalence 20.1%)	SE mix (SEA, SEC, TSST-1) sIgE (≥ 0.35 kU/L)	14.4% (16/111) in current wheeze; 14.9% (15/101) in physician-diagnosed asthma; 7.5% (23/307) in controls (never wheezer)

SE, Staphylococcus aureus enterotoxin; SEA-C, Staphylococcal enterotoxin A-C; TSST-1, toxic shock syndrome toxin-1; sIgE, specific IgE; ISAAC, the International Study of Asthma and Allergies in Childhood questionnaire.

However, it should be noted that the definition of SE positivity was considerably heterogeneous. To specify, 2 case-control studies (Bachert et al. [8] and Kowalski et al. [9]) and 2 population studies [12, 13] utilized the SE mix (Staphylococcal enterotoxin A [SEA], Staphylococcal enterotoxin C [SEC], toxic shock syndrome toxin-1 [TSST-1]) antigen kits; but three other case-control studies [14-16] used each enterotoxin sIgE tests (Table 1). Moreover, the cut-off value for positivity also varied. Two recent case-control studies (Bachert et al. [8] and Kowalski et al. [9]) adapted ≥ 0.1 kU/L, whereas other 5 previous case-control or population-based studies used ≥ 0.35 kU/L as the cutoff levels.

Considering the methodological heterogeneity, the pooled OR was calculated respectively for similarly designed study collection. For two case-control studies (Bachert et al. [8] and Kowalski et al. [9]) utilizing the cutoff of 0.1 kU/L for SE mix, the OR was 5.61 (95% CI 3.27-9.63); in three case-control studies (Lee et al. [14], Lee et al. [15] and Rossi and Monasterolo [16]) with different definition (as any of tested SE IgE ≥ 0.35 kU/L), the OR was 4.67 (95% CI 2.25-

http://dx.doi.org/10.5415/apallergy.2013.3.2.120

9.68). In two population-based studies (Hollams et al. [12] and Semic-Jusufagic et al. [13]), the pooled OR was relatively lower (OR 1.81, 95% CI 1.28-2.56) than case-control studies but was also significant. The OR for each study was presented in Fig. 2.

Specific findings

The studies by Rossi and Monasterolo [16] were conducted in allergic rhinitis and/or asthma patients with house dust mite sensitization. Particularly, they reported the correlation between SE sensitization and serum eosinophil cationic protein levels, indicating that SE sIgE is a potential marker for clinical severity of allergic diseases.

The studies by Lee et al. [15] in Taiwanese children/adolescents reported that the association with SE is more related to asthma or airway hyper-responsiveness (AHR) than allergic rhinitis alone. Lee et al. [14] also found significantly high prevalence of SE sensitization among Korean asthmatic adults. Additionally, they revealed that SE sensitization is related to the degree of AHR (methacholine PC20).

Two later case-control studies extend the previous findings to severe asthma. In the studies by Kowalski et al. [9], they found significantly higher serum levels of SE sIgE among severe asthmatics than nonsevere counterparts (1.39 ± 0.30 vs. 0.38 ± 0.07 kU/L; $p = 0.01$), despite similar rates of SE sIgE positivity (76.1% vs. 71.1%). They also found that the presence of SE sensitization

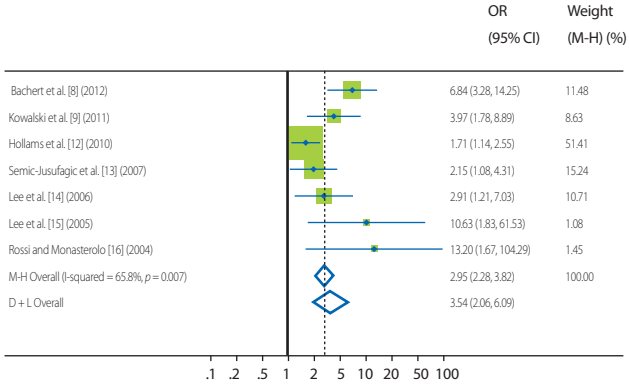

Fig. 2. Forest plots of studies comparing the frequency of Staphylococcal enterotoxin sensitization in asthmatics and controls. Green squares represent individual studies, and the size of squares is proportional to the number of subjects in the study. Horizontal lines indicate 95% confidence interval ranges. Vertical dotted lines and diamond shapes represent pooled summary estimates for the analysis (the width of the diamond represents the 95% CI).
OR, odds ratio; 95% CI, 95% confidence interval; M-H, Mantel-Haenzel test; D+L, DerSimonian and Laird method.

significantly correlated with various lung function parameters, when adjusted for age. In recent studies by Bachert et al. [8], the association between SE sensitization and severe asthma was clearly demonstrated by utilizing various sophisticated statistical models. Particularly, they found that SE sIgE was more closely related to asthma severity than house dust mite or grass pollen sIgE was.

Two population-based studies were available for children/adolescents; however, their associations with asthma were significant but less strong than the case-control studies. In the studies by Semic-Jusufagic et al. [13] on UK children aged 5 years, SE sensitization significantly correlated with current wheeze, wheeze frequency and persistence, and dry air bronchial reactivity. Later studies by Hollams et al. [12] on Australian children aged 14 years found dose-dependent relationships of SE-sIgE for asthma (in univariate analyses), and particularly for AHR (also in multivariate analyses).

Although not included in the present analyses, the studies by Tee and Pepys [17] were the first to compare sIgE to bacterial antigens (*S. aureus, Streptococcus pneumoniae* and *Haemophilus influenzae*) in subjects with various allergic diseases. The reasons for exclusion were that they did not define the positivity of SE sensitization in a standardized manner and did not report the prevalence of SE sensitization and thus were not directly comparable to other included studies. Methodologically, they utilized the radio-allergosorbent tests (RAST) and the RAST score ratio (= patient's specific RAST score/cord blood specific RAST score) for comparisons. In their reports, IgE RAST scores for *S. aureus* were slightly higher in asthmatics (n = 20, mean 1.2) than controls (n = 20, mean 1.0), but without statistical significance.

DISCUSSION

The present systematic review demonstrated that SE sensitization has significant associations with asthma. Particularly, it was suggested to have relationships with the clinical reactivity and severity of asthma by individual studies. The relationships have been consistently observed, despite methodological heterogeneity.

In the literature, the history of studies on the role of bacterial antigens for asthma go back to about 100 years ago [18]. Since then, numerous researchers have long been interested in the roles of bacteria, particularly *S. aureus*, in the pathogenesis of asthma

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but with controversy [17, 19-25]. It is just until recently that their significant associations have come into the spotlight.

In a sense, it is not surprising that *S. aureus* may contribute to the pathogenesis of asthma, as it has already been consistently associated with other allergic disorders like atopic dermatitis [6] or chronic rhinosinusitis with nasal polyp [7]. *S. aureus* has a peculiar characteristic to produce enterotoxins which act as superantigens, and thus exerts potent immunologic stimulatory effects on various immune cells [5]. Of note, Staphylococcal enterotoxin B (SEB) has been well demonstrated to have pro-allergic actions. *In vitro* experiments have revealed that SEB induces the corticosteroid insensitivity in human peripheral blood mononuclear cells [25], modulates dendritic cells to drive Th2 polarization [26], and influences nasal epithelium to secrete granulocyte migration and survival factors [27]. *In vivo* experiments have demonstrated that nasal SEB administration can promote allergen sensitization and airway inflammation in ovalbumin-induced murine asthma [28], or induce non-allergic eosinophilic asthma by itself [29]. In another animal model using epicutaneous SEB exposure, it enhanced ovalbumin-induced experimental 'atopic march' from dermatitis to asthma, supporting its pathophysiological plausibility [30].

Nevertheless, the direct role of *S. aureus* for asthma has been questioned, as it is a colonizer mostly in the upper airways and skins, but not in the lower airways [4]. Lower airways have long been considered to be sterile, and the invasion of pathogenic bacteria into the lower tracts may cause pneumonia not asthma. However, recent advances in metagenomics technologies have uncovered that lower airways, particularly in the subjects with asthma, are not sterile as previously thought, but rather have high burden of colonized bacteria [31, 32].

Still we do not have direct evidence that *S. aureus* causes asthma without causing pneumonia. However, we postulate the hypothesis that *S. aureus* has a mechanism to survive within the bronchial epithelium at small numbers and may secrete enterotoxins to promote various immunologic modulation. Theoretically, the survival could be more favorable in allergic subjects; as M2 macrophages are more frequent in allergic micro-environments, resulting in the decreased phagocytotic activity and the increased intracellular survival of microbes [33]. To prove this, it may be needed to directly compare the presence of *S. aureus* within the bronchial biopsy samples obtained from asthmatics and controls, with utilizing techniques such as peptide nucleic acid-fluorescence *in situ* hybridization (PNA-FISH). In a recent study using the epithelium from nasal polyps and PNA-FISH, *S. aureus* was found to be able to invade into the nasal epithelium and survive in patients with nasal polyposis [34, 35].

Another possible link between *S. aureus* and asthma could be the effects of chronic repeated spillover of low dose Staphylococcal exotoxins from the upper airways. About a quarter of individuals are known to have *S. aureus* colonization in their upper airways [4]. In subsets of subjects with genetically susceptible T-cell receptor β-variable region 8, the exposure to Staphylococcal enterotoxins may stimulate responsive immune cells and diseases [36]. Another genetic factor may be the *IL-5* promoter polymorphism [37].

Then, which asthma subtype would be more related to SE sensitization? To answer this, it needs to be examined in large scale unbiased population samples. Particularly, studies are still lacking on adult community populations. Based on the findings from the case-control studies [8, 9], older age is presumably a clinical factor to link asthma and SE sIgE. In older adult asthma, eosinophilic airway inflammation is frequently observed while no serum sIgE is detectable for common inhalant allergens. We speculate that Th2 responses to inhaled bacterial antigens may contribute to non-atopic eosinophilic asthma in older adults. Severe asthma is another subtype which is related to SE sIgE, as suggested by two recent case-control studies [8, 9].

There still remains possibility that SE sensitization is a 'surrogate marker' just to reflect the effects of still 'undiscovered risk factors'. In fact, *S. aureus* and various bacteria may co-exist in indoor dust [38], and its sensitization could be correlated with exposure to indoor dust, toxins or other pathogens. High indoor levels of bacteria and mold spores have already been associated with asthma severity [39]. Moreover, serum antibody levels do not directly represent the local inflammation in the airways. Further studies would be necessary to delineate whether it is a surrogate marker or the causative factor.

A limitation of this study should be considered in the interpretation of findings. All the included studies reported the positive associations between asthma and SE sensitization, which might be indicative of publication bias. Small numbers of included studies (n = 7) and substantial heterogeneity (I^2 = 65.8%) warrants careful interpretation of the results. Particularly in adults, large-scale community population-based studies are necessary to confirm the findings.

In conclusions, the systematic review and meta-analyses of current literatures demonstrated that Staphylococcal enterotoxin sensitization was significantly associated with asthma. These findings warrant further studies for elucidating mechanisms, and

http://dx.doi.org/10.5415/apallergy.2013.3.2.120

for confirming their relationships in large-scale populations.

ACKNOWLEDGEMENTS

We thank Professor Hae-Sim Park (Ajou University College of Medicine, Korea), Professor Jae-Young Lee (Hallym University College of Medicine, Korea), Professor Patrick Holt (University of Western Australia, Australia), and Professor Claus Bachert (Ghent University, Belgium) for data provision and kind advice. This study was supported by grants of Seoul National University Bundang Hospital and the Korean Health 21 R&D Project, Ministry for Health, Welfare and Family Affairs, R.O.K. (A030001).

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