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ORIGINAL ARTICLE

Nasal Carriage of *Staphylococcus aureus* does not affect the Clinical Response to Immunotherapy in Allergic Rhinitis Patients

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Key words:
Staphylococcus aureus, nasal carriage, allergic rhinitis, immunotherapy

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ABSTRACT

Background: *Nasal carriage of Staphylococcus aureus (NCSA) is frequent in patients with allergic rhinitis (AR). Allergen immunotherapy is safe and effective in the treatment of AR.* ***Objective:*** *The present work aims to assess the effect of NCSA on the clinical response to immunotherapy (IT) in AR patients.* ***Methodology:*** *Assessment of symptom severity was done by visual analogue scale in 25 NCSA-positive and 25 NCSA-negative AR patients. Patients were treated by cluster IT for 8 weeks after which symptom severity was reassessed.* ***Results:*** *Before IT, NCSA-positive patients showed significant increase in rhinorrhea, sneezing, and nasal blockage than NCSA-negative patients. No significant difference was observed in non-nasal symptoms or total symptom severity scores. After IT, there was no difference in the severity of nasal and non-nasal symptoms between the two groups. Clinical improvement was more noticeable in NCSA-positive than NCSA-negative patients; however, the difference is non-significant.* ***Conclusion:*** *NCSA does not affect the clinical response to immunotherapy in AR patients.*

INTRODUCTION

Allergic rhinitis (AR) is an inflammatory disease of the nasal mucosa characterized by infiltration of inflammatory cells and release of inflammatory mediators. Nasal *Staphylococcus aureus (S. aureus)* carriage is frequent in patients with perennial allergic rhinitis (PAR). *S. aureus* constitutes the main species of nasal flora in these patients[1]. It predominantly colonizes the anterior part of the nasal cavity by adhering to the surface structures of nasal mucosa and escaping the host innate and adaptive immune responses[2].

Nasal carriage of *Staphylococcus aureus* (NCSA) can potentiate allergic rhinitis through sensitization to staphylococcal enterotoxins leading to increased production of local IgE[3]. Staphylococcal toxins, which have a superantigenic activity, act locally by stimulating polyclonal T cell and B cell proliferation and causing class switching to immunoglobulin IgE leading to production of allergen-specific IgE by mucosal B cells[4]. Serum IgE antibodies to staphylococcal superantigens are also produced[5]. Moreover, *S. aureus* superantigens inhibit the activity of T regulatory cells that normally control inflammation[4].

Allergen-specific immunotherapy is the only currently available immune-modifying treatment for patients suffering from IgE-mediated diseases. It is effective in patients with PAR and, unlike anti-allergic drugs, has been shown to adapt the underlying cause of the disease with confirmed long-term benefits[6]. It is safe and effective in reducing both the symptoms and medication use in these patients[7].

Although several studies evaluated the effect of nasal carriage of *S. aureus* on the severity of allergic rhinitis, no studies were conducted to assess if nasal carriage of *S. aureus* affects the clinical response to immunotherapy for AR. This study compared the clinical response to IT in NCSA-positive and NCSA-negative AR patients to determine if it is affected by the nasal carriage of *S. aureus.*

METHODOLOGY

Patients and study design:

The study was conducted on patients with perennial AR attending the Allergy and Immunology Clinic of Suez Canal University Hospital. Patients of either sex with age ranging from 16 to 60 years were eligible for the study. AR was diagnosed by medical history, physical examination, prick skin test and measurement of serum total IgE. Patients sensitive only to house dust mite allergens (*Dermatophagoides pteronyssinus* and *Dermatophagoides farina)* were included in the study. Smokers, patients with other nasal diseases, and patients receiving corticosteroids or immunosuppressive therapy were excluded from the study. Ethics committee of Faculty of Medicine, Suez Canal University had reviewed and approved the study. Written informed consent was obtained from all study participants.

Nasal swabs were collected from all patients for diagnosis of *S. aureus* nasal carriage. According to the results of nasal swabs, the study was completed on 50 patients divided into two equal groups; 25 NCSA-positive patients and 25 NCSA-negative patients. Both

groups received allergen-specific cluster immunotherapy for 8 weeks. Assessment of nasal and non-nasal symptom severity was done before and after immunotherapy using a visual analogue scale (VAS).

Assessment of AR symptom severity:

Assessment of symptom severity of AR was done using a 1 to 10 visual analog scale (VAS) according to Klimek *et al.*[8] with 0 representing no symptoms and 10 representing the most severe symptoms. Assessed nasal symptoms were rhinorrhea, sneezing, nasal itching, nasal blockage, and postnasal drip. Assessed non-nasal symptoms were headache, eye symptoms, ear symptoms, throat symptoms, and sleep disturbance. The total score ranges from 0 to 50 for nasal symptoms and also for non-nasal symptoms.

Diagnosis of nasal carriage of S. aureus:

Nasal swabs were collected using sterile cotton swabs moistened with sterilized saline solution from the septum, floor, and lateral walls of the nose. Specimens were cultured on mannitol salt agar and incubated aerobically at 37°C for 24 hours. The suspected yellow colonies were identified as *S. aureus* based on morphology, Gram stain, catalase test, and coagulase test.

Protocol of immunotherapy:

Allergen-specific cluster subcutaneous immunotherapy (Omega, Montreal, Canada) was used for the treatment of patients according to the protocol of American Academy of Asthma Allergy and Immunology[9]. Treatment schedule lasted for 8 weeks and included 3 injections in each visit for the first 3weeks, 2 injections in each visit for the next 4 weeks and only one injection in the last week. The time interval between each two injections was 30 minutes. Table (1) shows the schedule of immunotherapy.

Table 1: Cluster immunotherapy schedule with the dose in milliliter (ml) and concentration as dilution of maintenance vial (AAAAI, 2011).

Visit	1st injection		2nd injection		3rd injection	
	Dose	Conc.	Dose	Conc.	Dose	Conc.
Visit (1)	0.10	1:1000	0.40	1:1000	0.10	1:100
Visit (2)	0.20	1:100	0.40	1:100	0.07	1:10
Visit (3)	0.10	1:10	0.15	1:10	0.20	1:10
Visit (4)	0.35	1:10	0.50	1:10	-	-
Visit (5)	0.07	1:1	0.10	1:1	-	-
Visit (6)	0.15	1:1	0.20	1:1	-	-
Visit (7)	0.30	1:1	0.40	1:1	-	-
Visit (8)	0.50	1:1	-	-	-	-

Statistical analysis

Statistical analysis was performed using statistical package for social sciences (SPSS) program (Version 17.0). All data were expressed as mean ± standard deviation (SD). The t test was used to compare the severity of AR symptoms between NCSA-positive and NCSA-negative patients. The level of significance was set at p value <0.05.

Clinical improvement was calculated as the percentage of decrease in the mean of symptom severity.

RESULTS

The 50 studied patients were 27 females and 23 males with mean age 19.6±7.5. Assessment of nasal symptoms severity before IT showed that there was a significant increase in the severity of rhinorrhea, sneezing, and nasal blockage in NCSA-positive patients than NCSA-negative patients ($p<0.05$). However, no difference was shown between them in nasal itching or postnasal drip. No significant difference was detected between the two groups in non-nasal symptoms or the total symptom severity scores. AR symptom severity score (SSS) in NCSA-positive and NCSA-negative patients before IT is shown in table (2).

Table 2: AR symptom severity score in NCSA-positive and NCSA-negative patients before IT by VAS

Symptoms	NCSA-positive patients	NCSA-negative patients	P value
Nasal:			
Rhinorrhea	6.94 ± 4.28	4.35 ± 3.26	< 0.05*
Sneezing	7.12 ± 5.44	4.52 ± 3.41	< 0.05*
Nasal itching	4.25 ± 3.98	3.85 ± 4.09	> 0.05
Nasal blockage	6.57 ± 4.92	4.38 ± 2.33	< 0.05*
Postnasal drip	3.22 ± 2.14	3.18 ± 2.27	> 0.05
Total nasal SSS	28.10 ± 4.15	20.28 ± 3.07	> 0.05
Non-nasal:			
Headache	5.82 ± 4.16	5.46 ± 3.37	> 0.05
Eye symptoms	2.17 ± 1.81	2.42 ± 2.06	> 0.05
Ear symptoms	3.26 ± 2.55	3.89 ± 2.18	> 0.05
Throat symptoms	2.34 ± 2.09	2.54 ± 1.88	> 0.05
Sleep disturbance	1.48 ± 2.97	1.39 ± 2.56	> 0.05
Total non-nasal SSS	15.07 ± 2.72	14.70 ± 2.79	> 0.05

*Significant

After allergen immunotherapy, NCSA-positive patients showed significant decrease in the severity of all nasal and non-nasal AR symptoms except for sleep disturbance which showed non-significant increase. Also, the decrease in the total severity scores of nasal and non-nasal symptoms was significant ($p < 0.001$). The clinical improvement in nasal symptoms was 35.2% and in non-nasal symptoms was 15.7%. AR symptom severity scores in NCSA-positive patients before and after IT are shown in table (3).

Table 3: AR symptom severity score in NCSA-positive patients before and after IT

Symptoms	Before IT	After IT	P value
Nasal:			
Rhinorrhea	6.94 ± 4.28	2.54 ± 1.12	< 0.001*
Sneezing	7.12 ± 5.44	2.26 ± 2.04	< 0.001*
Nasal itching	4.25 ± 3.98	1.31 ± 1.58	< 0.05*
Nasal blockage	6.57 ± 4.92	2.56 ± 1.63	< 0.001*
Postnasal drip	3.22 ± 2.14	1.84 ± 0.98	< 0.05*
Total nasal SS	28.10 ± 4.15	10.51 ± 1.47	< 0.001*
Non-nasal:			
Headache	5.82 ± 4.16	2.43 ± 1.39	< 0.001*
Eye symptoms	2.17 ± 1.81	1.24 ± 1.05	< 0.05*
Ear symptoms	3.26 ± 2.55	1.37 ± 1.28	< 0.05*
Throat symptoms	2.34 ± 2.09	1.42 ± 0.36	< 0.05*
Sleep disturbance	1.48 ± 2.97	0.74 ± 0.58	> 0.05
Total non-nasal SS	15.07 ± 2.72	7.20 ± 0.93	< 0.001*

**Significant*

In NCSA-negative patients, immunotherapy had led to a significant decrease in the severity of all nasal and non-nasal AR symptoms except for eye symptoms and sleep disturbance. Moreover, the decrease in the total severity scores of nasal and non-nasal symptoms was significant ($p < 0.001$). The clinical improvement in nasal symptoms was 21% and in non-nasal symptoms was 15.2%. AR symptom severity scores in NCSA-negative patients before and after IT are shown in table (4).

Table 4: AR symptom severity score in NCSA-negative patients before and after IT

Item	Before IT	After IT	P value
Nasal symptoms:			
Rhinorrhea	4.35 ± 3.26	1.92 ± 1.33	< 0.05*
Sneezing	4.52 ± 3.41	2.15 ± 1.84	< 0.05*
Nasal itching	3.85 ± 4.09	1.52 ± 0.87	< 0.05*
Nasal blockage	4.38 ± 2.33	2.44 ± 1.36	< 0.001*
Postnasal drip	3.18 ± 2.27	1.73 ± 0.88	< 0.05*
Total nasal SS	20.28 ± 3.07	9.76 ± 1.25	< 0.001*
Non-nasal symptoms:			
Headache	5.46 ± 3.37	2.52 ± 1.19	< 0.001*
Eye symptoms	2.42 ± 2.06	1.46 ± 1.37	> 0.05
Ear symptoms	3.89 ± 2.18	1.39 ± 1.28	< 0.001*
Throat symptoms	2.54 ± 1.88	1.27 ± 0.59	< 0.05*
Sleep disturbance	1.39 ± 2.56	0.48 ± 0.63	> 0.05
Total non-nasal SS	14.70 ± 2.79	7.12 ± 1.00	< 0.001*

**Significant*

Comparing the scores of symptom severity between the NCSA-positive and NCSA-negative patients after IT revealed that there was no difference in the symptom severity between the two groups regarding both the nasal and non-nasal symptoms (P>0.05). Clinical improvement was more noticeable in NCSA-positive patients than NCSA-negative for nasal symptoms (35.2% vs. 21%) but comparable to each other for non-nasal symptoms (15.7% vs. 15.2%), however, the difference is non-significant. The symptom severity scores in the two groups after finishing the course of immunotherapy is shown in table (5).

Table 5: AR symptom severity scores in NCSA-positive and NCSA-negative patients after IT

Symptoms	SAC-positive patients	SAC-negative patients	*P value
Nasal:			
Rhinorrhea	2.54 ± 1.12	1.92 ± 1.33	
Sneezing	2.26 ± 2.04	2.15 ± 1.84	
Nasal itching	1.31 ± 1.58	1.52 ± 0.87	
Nasal blockage	2.56 ± 1.63	2.44 ± 1.36	> 0.05
Postnasal drip	1.84 ± 0.98	1.73 ± 0.88	
Total nasal SS	10.51 ± 1.47	9.76 ± 1.26	
Improvement in SS	35.2%	21%	
Non-nasal:			
Headache	2.43 ± 1.39	2.52 ± 1.19	
Eye symptoms	1.24 ± 1.05	1.46 ± 1.37	
Ear symptoms	1.37 ± 1.28	1.39 ± 1.23	
Throat symptoms	1.42 ± 0.36	1.27 ± 0.59	> 0.05
Sleep disturbance	0.74 ± 0.58	0.48 ± 0.63	
Total non-nasal SS	7.20 ± 0.93	7.12 ± 1.00	
Improvement in SS	15.7%	15.2%	

**P value > 0.05 is non-significant*

DISCUSSION

Nasal carriage of *S. aureus* (NCSA) contributes to airway inflammation and allergic response in patients with allergic rhinitis. Allergen IT induces clinical and immunological tolerance in allergic patients as demarcated by persistence of clinical benefits and associated long-term immunological parameters after discontinuation of therapy[10]. This work studied the clinical response to allergen IT in NCSA-positive and NCSA-negative PAR patients to assess if this response is affected by nasal carriage of *S. aureus.*

Assessment of nasal symptoms severity before IT showed that there was a significant increase in rhinorrhea, sneezing, and nasal blockage in NCSA-positive patients than NCSA-negative patients, but no difference was shown between them in nasal itching or postnasal drip. No significant difference was detected

between the two groups regarding non-nasal symptoms or the total symptom severity scores. Riechelman et al. reported that symptom scores for nasal obstruction, hypersecretion and irritation were insignificantly higher in allergic nasal *S. aureus* carriers when compared with allergic non-carriers[11]. Shiomori et al. [12] also found that the nasal symptom scores were significantly higher in the *S. aureus*-positive group compared with the *S. aureus*-negative group. Also, Refaat et al.[3] found a positive correlation between nasal *S. aureus* counts and sneezing. Cevik et al.[13] stated that NCSA may be important not only in terms of AR-related disorders but also in their complications and co-morbidities in comparison to healthy subjects.

Several studies were conducted to explain the relationship between NCSA and AR. Some reported that NCSA potentiate allergic rhinitis through sensitization to *S. aureus* enterotoxins leading to increased production of local and serum IgE[3,14]. Others found that it is allergic rhinitis which may lead to change in the nasal flora leading to colonization with *S. aureus* which may be due to accumulated allergic responses against sensitized allergens[15] or partly due to increased hand-to-nose contact caused by blowing, picking, or rubbing[12,16]. However, Tylor et al. [17] found no difference in quantitative and qualitative bacterial flora in nasal cavity between PAR patients and non-allergic rhinitis subjects.

After immunotherapy, all patients included in this study showed significant difference in nasal symptoms. For non-nasal symptoms, they showed significant difference except for sleep disturbance in NCSA-positive patients and eye symptoms and sleep disturbance in NCSA-negative patients. Purkey et al. [18] reported that subcutaneous IT improves symptoms, medication scores and quality of life measures in AR patients. Petalas and Durham[19] also found that injection immunotherapy is a safe treatment for AR provided that it is delivered with a harmonious interaction between appropriately selected patients and trained medical personnel. However, Eifan et al. [20] studied the clinical efficacy of allergen immunotherapy for house dust mite and reported that more trials are needed before HDM subcutaneous immunotherapy can be recommended in routine practice for allergic rhinitis and/or asthma.

Comparing the symptom severity between the NCSA-positive and NCSA-negative patients after IT showed that clinical improvement was more noticeable in NCSA-positive patients than NCSA-negative for nasal symptoms (35.2% vs. 21%) but comparable to each other for non-nasal symptoms (15.7% vs. 15.2%), however, the difference is non-significant for both nasal and non-nasal symptoms. This may be explained by the initial more severe nasal symptoms in NCSA-positive patients before IT especially rhinorrhea, sneezing and nasal blockage. Because NCSA does not affect the clinical response to immunotherapy for AR, eradication of the NCSA state before IT is not mandatory, especially that its eradication may be difficult in some cases. Ou et al. [21] found that *S. aureus* is able to escape from host detection and resides within the sinonasal mucosa despite intense treatment. Zeldin et al.[22] revealed that eradication of the NCSA state has no effect on clinical improvement of PAR. However, Refaat et al.[3] recommended early detection and treatment of *S. aureus* carriage in AR patients. Bae et al.[23] also recommended a better understanding of the colonization and interaction of potential respiratory pathogens for designing control strategies that target bacterial colonization in upper respiratory tract.

CONCLUSION

In spite that nasal carriage of *S. aureus* increases the severity of symptoms of allergic rhinitis, this carriage has no effect on the clinical response to immunotherapy for AR, and both the NCSA-positive and NCSA-negative patients can get comparable benefits from that modality of treatment.

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