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Prevalence of Nasal Carriage of Staphylococcus aureus in Chronic Spontaneous Urticaria and Its Association with Disease Control Status

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ABSTRACT

Introduction:
Chronic spontaneous urticarial (CSU) is characterized by the appearance of erythematous, pruritic plaques or papules with superficial swelling of the dermis, which is recurring for more than six weeks and for which no underlying condition of external etiology is found. Nasal carriage for Staphylococcus aureus has been suggested to be significantly more frequent among CSU patients. This study was designed to compare Staphylococcus aureus prevalence in urticaria and control patients and evaluate a possible correlation between nasal carriage for S. aureus and CSU control.

Materials and Methods:
A population of 60 confirmed CSU cases and 30 healthy controls not working in a health-care-related environment were randomly recruited. Nasal swabs and cultures were done for all individuals. Controlled and poorly controlled urticarial was defined by UCT. S. aureus-positive CSU patients received treatment regarding their S. aureus colonization.

Results:
About 26.7% of CSU cases and 6.7% of healthy controls were nasal carriers for S. aureus, and the difference in the frequency was statistically significant (P = 0.025). 81.3% S. aureus positive of CSU patients and 84.1% of S. aureus negative patients (n=37) had a poorly controlled disease, and the difference was not statistically significant (P = 0.99).

Conclusion:
Nasal carriage for S. aureus is more frequent among CSU patients compared to healthy controls. However, being a carrier for S. aureus does not have a detrimental effect on the disease control status of CSU patients.

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Introduction

Chronic spontaneous urticarial (CSU) is characterized by the appearance of erythematous, pruritic plaques or papules with superficial swelling of dermis edema of the skin and mucosal membranes that is recurring for more than six weeks and for which no underlying condition of external etiology is found. CSU comprises about 80 percent of chronic urticarial cases.

The effect of chronic urticaria on patients' quality of life can be grave. Therefore, finding potential modifiable etiological factors can be of great importance. Several factors have been suggested as possible etiology for CSU, but in most cases, the etiology cannot be found even after extensive workup. Food allergens, autoimmunity, drugs, hormone levels (serotonin), neurotransmitters (substance P), severe psychological stress, chronic infection, and so forth have been studied as possible triggers of chronic urticaria (1-3).

Several studies have evaluated the association between infections and chronic urticaria. Although acute viral infections seem to have more of an aggravating effect on the course of chronic urticaria than triggering, chronic bacterial infections have also been studied as a potential etiological factor in some cases of chronic urticaria (4). Although the exact mechanism of infection-induced urticaria is not well known, several mechanisms have been postulated, such as triggered histamine and leukotrienes release from the mast cells (5).

Among bacterial agents leading to urticaria, Helicobacter pylori has drawn significant interest and has been studied further than other agents.

In a study conducted in 2015 by Mogaddam et al., the authors found a correlation between chronic spontaneous urticaria and H. pylori infection, and more interestingly, they found that eradicating H. pylori alleviates symptoms of CSU patients (6). In another study conducted by Kohli et al. in 2018, it was found that chronic urticaria patient who has subclinical Helicobacter pylori infections have a higher mean urticaria severity score, number of urticaria/ angioedema recurrences per year, and higher number of involved body parts when compared to chronic urticaria patients without H. pylori infection. However, the correlation was not statistically significant (7). In another study, Sharma et al. found that H. pylori infection is not more frequent in CSU patients than in a healthy population (5).

However, they found that when the eradication regimen for H. pylori is added to the primary antihistaminic treatment in urticaria patients, a statistically significant improvement is observed in clinical symptoms of CSU patients compared to both CSU patients who did not receive the eradication regimen and patients who were not infected (8).

More interestingly, a study conducted by Zheleznov et al. found that upper gastrointestinal inflammatory disorders can both cause CSU and trigger exacerbations irrespective of H. pylori infection (9).

Staphylococcus aureus (S. aureus) is a Gram-positive, round-shaped bacterium that belongs to the Firmicutes and is a typical member of the body's flora commonly found in the upper respiratory tract and on the skin. While S. aureus typically functions as a human microbiota commensal, it may also become an opportunistic pathogen, a widespread cause of skin infections such as abscesses, respiratory diseases, and food poisoning (10).

Skin infections are the most common form of S. aureus infection manifesting in various ways, such as small benign boils, folliculitis, impetigo, cellulitis, and more severe, invasive soft-tissue infections (11). It has been shown that S. aureus nasal carriage rates are about 26-28% in the normal population (12,13).

S. aureus is particularly frequent in individuals with atopic dermatitis, most generally known as eczema. It is often present in moist, active areas, including hair, armpits, and scalp. (14,15). Colonization of S. aureus causes inflammation of atopic dermatitis. S. aureus is thought to exploit skin barrier defects in people with atopic dermatitis, trigger cytokine expression, and thus exacerbate the symptoms (14,5).

S. aureus has also been studied in CSU. Nasal carriage for S. aureus is more frequent in CSU patients than in healthy controls (16). More interestingly, another study found that not only nasal carriage for S. aureus is more common among CSU patients compared to healthy controls; however, antimicrobial

treatment targeting S. aureus resulted in complete recovery from urticaria in some CSU patients who were a nasal carrier for S. aureus (7). Also, Sharma et al. found that eradication therapy for S. aureus nasal carriage resulted in complete recovery in 28.12% and partial recovery in 12.5% of their chronic urticarial patients; however, 59.37% of their patients were still suffering from chronic urticarial six weeks after the treatment based on their post-treatment urticarial activity score (7).

In an attempt to find a mechanism through which S. aureus exerts its effect in CSU patients, researchers have found that IgE against staphylococcal enterotoxins is not only more common in CSU patients compared to the general population, but also their levels strongly correlate with disease activity (17). We hypothesized that not only S. aureus is more prevalent in CSU patients compared to the general population, but it also has a detrimental effect on the severity of urticaria. This study aims to evaluate the prevalence of nasal carriage for S. aureus in CSU patients and its effect on disease control status.

Materials and Methods

Patient Selection:

A case-control study was conducted between March 21st, 2016, and March 21st, 2017. The study population included patients diagnosed with CSU by an allergy subspecialist at allergy and clinical immunology clinics. CSU was defined as urticarial lesions that recur longer than six weeks and for which no underlying and external etiology was found.

These patients were referred to our immunology laboratory after signing informed consent.

As for the control group, healthy individuals who were not working in a health-care-related environment were included. Individuals with a diagnosis of an infectious, autoimmune, allergic, or inflammatory condition and subjects with a recent history of any pharmacologic intervention (especially recent antibiotic therapy) were excluded from our study. Ninty individuals were enrolled in this study, of whom 60 and 30 belonged to case and control groups, respectively.

Data Acquisition

The Statistical population included individuals who completed two questionnaires at the beginning of the study. The first questionnaire included questions regarding the demographic data (age, sex, disease duration, marriage status, and last educational degree), recent history of taking antihistamines, and the results of the patient's latest white cell count (WBC) and also differential and erythrocyte sedimentation rate (ESR) which prepared by the laboratory. The second questionnaire was the Urticaria Control Test (UCT), completed only by the individuals in the case group. A score of 12 or more was considered controlled urticaria, and a score under 12 was considered poorly controlled urticaria.

Bacteriologic Methods and Materials

A nasal swab was obtained using a sterile swab from all included individuals, and specimens were transferred to the Trypticase soy broth (TSB) media before being transferred to the laboratory. The Maximum transfer time of the specimen was 6 hours. After arriving at the laboratory, specimens were immediately cultured in Sheep Blood Agar and MacConkey agar media. All media were incubated at 37 degrees Celsius and were evaluated after 24 and 48 hours. At these time points, gram-positive bacteria from gram-positive colonies were isolated and gram-stained. Then, the Staphylococci were isolated. Tube and slide coagulase tests were used to isolate Staphylococcus aureus from coagulase-negative Staphylococci (CoNS). We then treated all CSU patients with a positive culture for S. aureus with Clindamycin (100 milligrams weekly).

Statistical Analysis

Statistical analyses were conducted using Kolmogorov-Smirnov, Fisher's exact test, Mann-Whitney, T-test, and Chi-square. The Kolmogorov-Smirnov test was used to determine normal distribution. Parametric and non-parametric tests were used in the case of the normal and non-normal distribution, respectively.

A ρ-value of <0.05 was considered as statistically significant. Statistics were

calculated using SPSS® Statistics (version 16.0. Chicago, SPSS Inc.).

Ethical Considerations

This study was presented to the organizational ethics committee of Mashhad University of Medical Sciences on December 21st, 2016 (study code: 950588).

All the participants signed an informed consent and could leave at any time during the study. Questionnaires were filled out using a number instead of names to protect individual's privacy.

Results

Patients characteristics

The CSU patient's ages ranged from 6 to 62 years and 12 to 76 years in control groups, respectively. 65.0% of CSU patients and 56.7% of the control group were female. Neither age nor sex was distributed significantly differently between the two groups (ρ-value>0.05) (Table 1).

Table 1. Patient's basic characteristics

		Total	CSU	Controls	ρ-value
Age		34.8 ± 13.4	34.6±11.9	35.2±15.9	0.868†
Sex	female	56 (62.2%)	39 (65%)	17 (56.7%)	0.442‡
	male	34 (37.8%)	21 (35%)	13 (43.3%)	

Data are presented as Mean ± SD or n (%). † Based on Independent sample T-test. ‡ Based on the Chi-Square test.

S. aureus Nasal Carriage and Chronic Spontaneous Urticaria

The prevalence of nasal carriage for S. aureus and CoNS in CSU patients was compared with those of the control group and is shown in Table 2. The difference between the prevalence of CoNS nasal carriage in CSU patients and controls was 10%, which was not statistically significant (ρ-value>0.05).

On the other hand, the frequency of S. aureus was significantly higher in CSU patients (ρ-value<0.05). Moreover, the odds of S. aureus nasal carriage positive in CSU patients were 5.01 times of the control group.

Table 2. Distribution of S. aureus nasal carriage in CSU patients and controls.

		Total	CSU	Controls	ρ-value
CoNS	positive	27 (30.0)	16 (26.7)	11 (36.7)	0.329‡
	negative	63 (70.0)	44 (73.3)	19 (63.3)	
S. aureus	positive	18 (20.0)	16 (26.7)	2 (6.7)	0.025‡
	negative	72 (80.0)	44 (73.3)	28 (93.3)	

Data are presented as n (%). ‡ Based on the Chi-Square test.

S. aureus Nasal Carriage and Disease Control Status

Based on the urticarial control test, 18.8% of CSU patients with S. aureus nasal carriage had poorly controlled urticaria, while this quantity in the control group was 15.9% (Table 3).

Overall, S. aureus nasal carriage was not associated with poorly controlled urticaria (ρ-value>0.05).

Table 2. S. aureus nasal carriage and disease control status

		Median (IQR)	Poorly controlled*	controlled**	ρ-value
S. aureus	positive	9 (4)	13(81.3)	3(18.8)	0.99‡
	negative	6.5 (6.5)	37 (84.1)	7 (15.9)	

** poorly controlled: score <12 on urticarial control test.** controlled: score ≥12 on the urticarial control test. ‡ Based on Fisher's exact test.*

Eight of sixteen CSU S. aureus nasal carriers were available a year after the end of the study for renewed nasal swab culture test. Interestingly, two scored 16 on UCT even though none did before treatment for S. aureus colonization. However, this should be interpreted with caution as this could be due to factors other than antibiotic treatment like

spontaneous resolution, other possible drugs consumed by the patient, and even other possible effects of Clindamycin and not the treatment for S. aureus colonization alone.

Discussion

Chronic bacterial infections are known to be associated with some cases of acute urticaria, and the diagnosis of these foci has been effective in some cases of urticaria, but not in all cases (18,19). Concerning the pathogens identified in chronic urticaria, some mechanisms for recurrent infections with Helicobacter pylori, streptococci, staphylococci, and yersinia have been defined (20,21). Regarding bacterial infections, Calado et al. have shown streptococcal tonsillar infection contributes to CSU that improves after antibiotic therapy (22). It is unknown what mechanism of infection leads to the initiation, perpetuation, or worsening of CSU. Different components of the immune response to infection may be responsible for different combinations at these various stages of CSU (23). Research published in 1967 described 15 out of 16 children with chronic urticaria who have chronic upper respiratory infections, tonsillitis, pharyngitis, otitis, sinusitis, and sometimes due to staphylococci or streptococci. Urticaria remission following antibiotic therapy was frequently noted, which is in keeping with our clinical experience in children (20,24-26). Nevertheless, studies have shown that chronic bacterial infection does not play a crucial role in the aetiology of chronic urticaria. Recent data showed that Staphylococcus aureus has a higher nasal carriage in patients with chronic urticaria compared to controls, indicating that nasal carriage is more common. In addition, a subpopulation of patients with chronic urticaria has been shown to have TSST, SEA, and SEB serum IgE antibodies (16,24). Sharma et al. have shown that from a population of 32 patients with S. aureus detected in their swab specimens from the nasal cavity, after the antimicrobial treatment, only 28.12% had shown complete recovery from urticaria during the follow-up period12.5% showed partial recovery from urticarial. In contrast, 59.37% continued to suffer from urticaria (5). In this study, we have found that nasal carriage for S. aureus is slightly more frequent in CSU patients than in healthy controls, and this difference in frequency does not exist for CoNS. It may be due to a potential etiological relationship between nasal carriage for S. aureus and chronic spontaneous urticarial specifically. We also observed that CSU patients who tested positive for S. aureus nasal carriage do not score significantly lower on the UCT results, implying S. aureus colonization is not associated with a deteriorating effect on CSU patients' disease control status. Regarding these findings, our study is not congruent with previous studies on the finding that nasal carriage for S. aureus is significantly more frequent in CSU patients than healthy controls and that nasal carriage of S. aureus can act as an etiological factor in chronic urticaria (5,16). In our study, we assessed colonization with CoNS as well, and our results confirm that the association between nasal carriage and chronic urticaria is specific to S. aureus and not all of Staphylococci. It can potentially have etiological implications since S. aureus produces some proteins that are exclusive to them, and targeting these proteins can be of therapeutic importance. Hence, one can conclude that nasal carriage of s.aureus can act as an etiological factor only in some cases of chronic urticaria. Our suggestion for future studies is to also assess the disease control status of their CSU patients in consecutive and short follow-up periods after initiation of treatment to see whether or not treating for S. aureus colonization affects the control status of the patient's urticarial.

Conflict of interest

The authors state that the research was carried out in the absence of any potential conflict of interest.

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