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Investigation of the relationship between anosmia in patients with COVID-19 and allergic rhinitis and eosinophil levels

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Abstract

Anosmia is a common symptom of COVID-19 infection. In our study, we aimed to investigate the relationship between allergic rhinitis and eosinophil levels in patients who developed anosmia after COVID-19 infection. Patients who had experienced COVID-19 infection and subsequently developed anosmia were included in the study group, while those who had experienced COVID-19 infection but did not develop anosmia were included in the control group. The patients' allergy histories and eosinophil levels were retrospectively analyzed. Our study revealed a significant difference in eosinophil levels between patients with and without anosmia ($p < 0.05$). Additionally, among 55 patients with pre-existing allergic rhinitis, 43 (78.2%) had normal or high eosinophil levels. There was no significant relationship found between age, gender, the most common presenting symptom, hospitalization status, presence of allergic rhinitis and asthma before COVID-19 and increase in allergic symptoms after COVID-19 infection, in patients with and without anosmia. While we did not find a relationship between the presence of allergic rhinitis and the development of anosmia, our study did show that eosinopenia is more pronounced in patients with anosmia. Furthermore, it has been suggested that eosinopenia may not be a suitable marker for patients with allergic symptoms before COVID-19, as these patients may have normal or high eosinophil levels.

Keywords: COVID-19, anosmia, allergy, eosinophil level

Introduction

The COVID-19 is an infectious illness that is caused by the SARS-CoV-2 virus. This virus rapidly spread across the globe, leading to its declaration as a global pandemic by the World Health Organization (WHO) on March 11, 2020. Anosmia is one of the prominent symptoms of COVID-19. While impaired sense of smell has been observed in other viral infections such as parainfluenza, rhinovirus, SARS, and others, its occurrence is much less frequent compared to SARS-CoV-2 infection. In most patients, sudden loss of smell can happen without any

accompanying symptoms, although occasional nasal congestion or a runny nose may be present. Mild symptoms like a dry cough can also be observed prior to the onset of anosmia [1,2].

Initially, it was expected that individuals with chronic respiratory diseases would have a higher mortality and morbidity rate during the early stages of the COVID-19 pandemic compared to the general population. It has been observed that the prevalence of asthma and allergic diseases among COVID-19 patients is lower than initially expected. These findings suggest that having asthma does not appear to be a significant risk factor for susceptibility

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to COVID-19. Additionally, allergic rhinitis and eczema have been associated with lower rates of hospitalization in relation to COVID-19 [3]. There is no evidence to suggest that patients with allergic rhinitis are at a higher risk of experiencing severe complications during a COVID-19 infection [4].

Eosinophil cells are a type of white blood cells found in the bloodstream and tissues, known for their strong pro-inflammatory effects in numerous diseases. Recent studies have shown that eosinophils have additional functions, including immune regulation and antiviral activity. Normally, eosinophils constitute a small percentage (1-3%) of circulating white blood cells. The presence of eosinophils is clinically significant due to their potent pro-inflammatory nature, primarily due to pre-formed granules containing cytotoxic proteins. Besides their pro-inflammatory effects, emerging evidence suggests that eosinophils also play regulatory roles in various physiological responses such as antiviral responses. In patients with severe respiratory distress syndrome caused by COVID-19, a decrease in eosinophil levels, known as eosinopenia, has been observed. Current evidence indicates that eosinopenia could potentially act as a predictive marker for a severe form of COVID-19 [5,6].

The aim of our study is to investigate the effect of the presence of allergic rhinitis and serum eosinophil levels on the anosmia in patients with COVID-19 infection.

Material and Methods

Our study was conducted with the approval of the Samsun Training and Research Hospital's non-interventional clinical research ethics committee under the permit number GOKA/2021/10/4. The study group consisted of patients who had contracted COVID-19 and subsequently experienced loss of smell, and who had presented to the Samsun Health Application and Research Center of SBÜ between April 1, 2020, and April 1, 2021. The control group was comprised of patients who had contracted COVID-19 but did not experience loss of smell, and who had

similar age and gender distributions to the study group. Patients who had not undergone a complete blood count test during the study period, had a history of nasal surgery, or had a history of smell loss prior to contracting COVID-19 were not included in the study. Demographic and clinical data, including age, gender, primary symptoms at admission, hospitalization status, history of allergic rhinitis and asthma prior to COVID-19 infection, increase in allergic symptoms after COVID-19 infection, presence of cacosmia, and eosinophil percentages in complete blood counts taken during the COVID-19 infection period, were retrospectively evaluated. The continuous variables were presented as mean ± standard deviation (SD), while categorical variables were presented as numbers and percentages. All statistical tests conducted were two-tailed, and a significance level of P<0.05 was considered statistically significant. The statistical analyses were carried out using SPSS® version 26.

Results

In total 27 patients were reviewed in this retrospective study, In our study, we enrolled a total of 169 patients, with 104 of them being female and 65 being male. The mean age of the participants was 38.86±10.56 years, ranging from 20 to 78 years. Among them, 83 patients had loss of smell, while the control group of 86 patients did not. Of the patients, 37 were treated in the hospital (%21.9), while 132 were treated on an outpatient basis (%78.1). Before contracting COVID-19, 55 patients had a history of allergic rhinitis (%32.5), and 22 had a diagnosis of allergic asthma (%13). After contracting COVID-19, 41 patients (%24.3) showed an increase in allergic symptoms. The mean eosinophil count in the complete blood count was 1.51±1.79 (range: 0.0-11.80). Eosinophil counts of %1-3 were considered normal, and counts lower than <%1 were considered eosinopenia. Among the 41 patients with loss of smell, 49.4% had eosinopenia, while among the 37 patients without loss of smell, 43% had normal or high eosinophil counts. Of the 55 patients with a history of allergic rhinitis, 49% had loss of smell, and 78.2% had normal

Table 1. Onset and recovery times of anosmia in patients with olfactory dysfunction

	Mean±SD (days)	Minimum-maximum duration (days)
Onset of anosmia	3.33±2.23	1-15
Recovery time of anosmia	33.68±51.56	4-270

or high eosinophil counts. Eosinopenia was detected in only 12 patients (%21.8) with a history of allergic rhinitis. Among the 83 patients in the study group, 92.8% (n=77) had their loss of smell resolved, while 7.2% (n=6) continued to have loss of smell. The onset and recovery times of loss of smell in these patients are summarized in Table 1.

When variables were compared between patients with and without olfactory dysfunction, no significant relationship was

found in terms of mean age, hospitalization rates, allergic rhinitis, and asthma. However, there was a significant difference in eosinophil counts between the two groups, with lower mean eosinophil counts in patients with olfactory dysfunction (p=0.046). The most common symptoms among patients at presentation were fever, sore throat, nasal congestion, and runny nose in both groups. In 17 patients (20.5%), kakosmia developed after resolution of olfactory dysfunction (Table 2).

Table 2. Analysis of variables between patients with and without anosmia

	With anosmia n (%)	Without anosmia n (%)	p
Gender			0.355
Female	54 (65.1)	50 (58.1)	
Male	29 (34.9)	36 (41.9)	
Pre-COVID allergic rhinitis			0.997
Yes	27 (32.5)	28(32.6)	
No	56 (67.5)	58(67.4)	
Pre-COVID asthma			0.315
Yes	13 (15.7)	9 (10.5)	
No	70 (84.3)	77 (89.5)	
Post-COVID allergy increase			0.081
Yes	25 (30.1)	16 (18.6)	
No	58 (69.9)	70 (81.4)	
Most common symptom			
Fever	30 (36.1)	21 (24.4)	
Sore throat	18 (21.7)	17 (19.8)	
Nasal congestion/runny nose	5 (6.0)	7 (8.1)	
Cough/shortness of breath	14 (16.9)	1 (15.1)	
Headache	7 (8.4)	7 (8.1)	
Joint pain-fatigue	4 (4.8)	21 (24.4)	
Loss of taste-smell	5 (6.0)	0 (0.0)	
Eosinophil levels	1.24±1.27 (mean±SD)	1.78±2.16 (mean±SD)	0.046
Age	37.73±10.60 (mean±SD)	39.95±10.48 (mean±SD)	0.173

Discussion

Post-infectious anosmia, characterized by the loss of smell, is primarily caused by upper respiratory tract infections and accounts for approximately 30-40% of anosmia cases. Various pathogens, with viruses being the most common, can contribute to this condition. The exact underlying mechanisms of post-infectious anosmia are not fully understood. It is believed to arise from an inflammatory reaction in the nasal mucosa, but in COVID-19 patients, anosmia can occur without significant rhinological symptoms or notable nasal inflammation [7,8]. Research suggests that viruses can inflict damage to the olfactory neuroepithelium or central olfactory pathways, leading to anosmia. In cases of post-infectious olfactory dysfunction, spontaneous recovery is observed in approximately 32-66% of patients within 1-3 years, whereas the short-term recovery rate in COVID-19 patients ranges from approximately 44% to 74% [8].

In a retrospective study conducted by Klopfenstein et al., anosmia symptoms were observed in 54 out of 114 COVID-19 patients, accounting for 47% of the cases. The study revealed that patients typically experienced anosmia approximately 4.4 days after the onset of infection. Additionally, it was found that 98% of patients recovered from anosmia within 28 days [9].

Another study conducted at Mayo Clinic used artificial intelligence methods to analyze the clinical features of COVID-19. This study discovered that the occurrence of loss of sense of smell,

was 28.6 times higher in COVID-19 positive patients compared to those who tested negative for COVID-19 [10].

In our study, it was determined that out of the 83 patients with anosmia, 77 of them (92.8%) experienced a resolution of their anosmia. The average duration of anosmia onset was found to be 3.33±2.23 (1-15) days, while the average duration of recovery from anosmia was 33.68±51.56 (4-270) days.

According to Naziroğlu and Aksu's study, there is no association between being atopic and the severity of COVID-19 [3]. The ACE2 and transmembrane serine protease 2 (TMPRSS2) receptors play a crucial role in facilitating the entry of the COVID-19 virus into cells. These receptors interact with the spike proteins of the virus. In a study conducted during the early stages of the COVID-19 pandemic, it was observed that the expression of the angiotensin-converting enzyme 2 (ACE2) gene, which is the receptor that the SARS-CoV-2 virus uses to enter human cells, was reduced in the respiratory airways of patients with asthma and respiratory allergies [11]. Moreover, some studies have suggested that the lungs may be the primary target organ for COVID-19 due to lower expression levels of ACE2 and TMPRSS2 proteins in the respiratory epithelial cells of the nasal cavity compared to the lower respiratory organs [8].

In our study, it was found that 55 patients (32.5%) had allergic rhinitis before contracting COVID-19 infection, and 22 patients (13%) had a diagnosis of allergic asthma. Additionally, it was

determined that there was an increase in allergic symptoms after COVID-19 infection in 41 patients (24.3%). However, no significant relationship was found between the presence of allergic rhinitis and asthma, and the occurrence of increased allergic symptoms after COVID-19 infection among patients with or without smell loss.

Rosenberg et al. have suggested that eosinophils play a dual role in the respiratory tract. While they contribute to the antiviral response against certain respiratory viruses, their elevated counts and/or activation status can lead to an excessive immune reaction and tissue damage in allergic diseases [12].

In a study conducted by Azkur et al. involving 138 hospitalized patients, eosinopenia (low eosinophil count) was observed in 73 patients (52.9%). The study found that 70% of the COVID-19 group and only 16.7% of the non-COVID-19 viral pneumonia group had eosinophil counts below the normal range. The authors proposed that eosinophil counts below normal levels could serve as a valid biomarker for diagnosing COVID-19 [6].

Zhang et al. reported that 53% of hospitalized patients with COVID-19 exhibited eosinopenia at the time of admission [13]. Similarly, in a study by Du et al., which examined medical records of 85 fatal cases of COVID-19, it was found that 81% of the patients had absolute eosinophil counts below the normal range at the time of admission [14].

Liu et al. reported that patients who were treated with lopinavir initially experienced eosinopenia, and the improvement in eosinophil levels before discharge could serve as an indicator of clinical improvement. The exact pathophysiology of eosinopenia in COVID-19 is not yet fully understood, but it is suggested that multiple factors may be involved. These include inhibition of eosinophil release from the bone marrow, decreased eosinophil production, reduced expression of chemokine receptors/adhesion factors, and direct eosinophil apoptosis induced by cytokines released during acute infection [6,15].

In our study, when analyzing the variables between patients with and without anosmia, there was no significant difference in mean age ($p=0.173$). However, a significant difference was observed in eosinophil levels between patients with and without anosmia ($p<0.05$). Among the 55 patients with allergic rhinitis before COVID-19, 43 (78.2%) had normal or elevated eosinophil levels. Therefore, although there is evidence supporting the potential of eosinopenia as an early indicator in COVID-19, it should be kept in mind that patients with pre-existing allergic symptoms may have normal or elevated eosinophil levels.

Conclusion

In conclusion, our study did not find a relationship between the presence of allergic rhinitis and the development of anosmia. However, it was observed that eosinopenia is more prominent in patients with anosmia. Additionally, it is suggested that in allergic patients, eosinopenia may not occur during COVID-19 infection, but these findings need to be supported by further studies conducted on larger sample sizes.

Conflict of Interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical Approval

Our study was conducted with the approval of the Samsun Training and Research Hospital's non-interventional clinical research ethics committee under the permit number GOKA/2021/10/4.

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