Acute-phase reactants association with smell disorders in coronavirus disease 2019-infected patients

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Abstract

Objective: Olfaction is a complex sensory process that has not been fully investigated. In this study, we aimed at investigating whether there is an association between acute-phase reactants [C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), neutrophil-to-lymphocyte ratio (NLR), and serum ferritin] and the presence of smell disorders in coronavirus disease 2019-infected patients.

Patients and methods: A prospective study was conducted on 61 patients presented to the Otolaryngology Department with a confirmed diagnosis of coronavirus disease 2019 based on the real-time reverse transcription PCR between July 2020 and February 2021. Participants in this study were divided into two groups: group A (olfactory dysfunction group) and group B (nonolfactory dysfunction group). Group A was further subdivided into two subgroups after 3 months: olfaction-recovery subgroup and olfaction-no-recovery subgroup. Complete blood count with differential count, acute-phase reactants, and NLR were investigated and compared at two chronological intervals: 0 and 3 months of diagnosis.

Results: The levels of CRP, ESR and NLR were found to be significantly increased in olfactory dysfunction group (group A) at 0 interval compared with nonolfactory dysfunction group (group B) ($P = 0.003$, $0.001$, and $0.04$, respectively). After 3-month interval, CRP, ESR, serum ferritin, and NLR started to trend down in patients in group A who experienced complete recovery of smell disorders (olfaction-recovery subgroup). Compared with the olfaction-recovery subgroup, the olfaction-no-recovery subgroup showed higher levels of CRP and serum ferritin ($P = 0.01$ and $0.04$, respectively).

Conclusion: Increased levels of CRP, ESR, and NLR in patients with olfactory dysfunction suggest that they may play a role in the initiation of this symptom. Reduction of CRP and serum ferritin after 3 months from the onset of olfactory dysfunction can be a prognostic marker of smell recovery.

Keywords: Acute-phase reactants, Coronavirus disease 2019, Dysfunction, Neutrophil-to-lymphocyte ratio, Olfaction

1. Introduction

In the early phase of the current coronavirus disease 2019 (COVID-19) pandemic, several studies reported that smell disorders were one of the cardinal features of this disease. Smell disorders have been reported in 33–80% of patients with COVID-19 infection [1,2] and are reported to be associated with other upper respiratory tract infections at a rate of 11–40% [3,4].

The primary clinical distinction between COVID-19-related anosmia and anosmia seen in other upper respiratory tract infections is the sudden onset irrespective of presence of nasal blockage or discharge [5,6].

Smell abnormalities can be the initial and the only symptom of COVID-19 infection and usually show excellent recovery within a few weeks even without treatment in most cases. Despite the high incidence of smell disorders, the precise pathogenesis is still not yet interpreted [7–9].

Three different mechanisms have been postulated to rationalize the smell disorders in COVID-19-infected patients: loss of olfactory receptor neurons,
brain infiltration affecting olfactory centers, and damage to the support cells in the olfactory epithelium [1].

The increase in inflammatory and immune mediators not only appeared to be related to the development of the COVID-19 disease but also to disease prognosis. C-reactive protein (CRP) has been associated with disease development and is an early predictor for severe COVID-19 [10].

The neutrophil-to-lymphocyte ratio (NLR) is an inflammatory marker that can predict prognosis in patients with various cardiovascular diseases. Moreover, NLR has been reported in previous studies as a prognostic marker for patients with sepsis. For COVID-19-infected patients, NLR has been shown to be an independent risk factor to detect the disease severity [11,12].

Many researchers have indicated that hematological (NLR) and inflammatory parameters [CRP, erythrocyte sedimentation rate (ESR), and serum ferritin] can be used as predictive biomarkers for COVID-19 disease [10].

In this study, we aimed at investigating whether there is an association between acute-phase reactants (APRs) (CRP, ESR, NLR, and serum ferritin) and the presence of smell disorders in COVID-19-infected patients.

2. Patients and methods

This prospective study included 61 patients presented to the otolaryngology Department at a tertiary care institution with a confirmed diagnosis of COVID-19 based on the real-time reverse transcription (rRT) PCR between July 2020 and February 2021. All patients showed cure of COVID-19 after 2 weeks as evidenced by two consecutive negative rRT-PCR, 48 h apart. This study was performed in accordance with standards set by the Swedish Research Ethical Review Authority and with the 1964 Helsinki Declaration and its later amendments. This study was approved by the institutional review board (permit number 002-1344-821).

Participants in this study were divided into two groups:

Group A included 50 patients with COVID-19 with smell disorder as their only clinical manifestation. This group was later subdivided into two subgroups after 3 months: olfaction-recovery subgroup and olfaction-no-recovery subgroup.

Group B included 11 asymptomatic confirmed COVID-19 controls with history of recent exposure or contact to COVID-19-infected patients. Participants in this group were determined to have normal smell function by subjective statement and absence of history of sinonasal disease. The AAO–HNS Anosmia Reporting Tool [13] was administered to both groups.

After obtaining informed consent from the enrolled patients, complete blood count with differential count, APRs (CRP, ESR, and serum ferritin), and NLR were investigated and compared at two chronological intervals: 0 and after 3 months of diagnosis. The NLR was defined as the absolute count of neutrophils divided by the absolute count of lymphocytes determined from the complete blood count.

Patients who manifested with symptoms other than olfactory disorders during the course of the study, pediatrics, pregnant patients, patients with a history of head trauma, pre-existing smell and taste alterations for any other reason, allergic rhinitis, and chronic rhinosinusitis were excluded. For group B (control group), any patient who developed upper respiratory symptoms or olfactory dysfunction during the course of the study was excluded.

All patients in group A tried olfactory training, saline nasal irrigation, and systemic omega 3 supplements as recommended by Whitcroft and Hummel [14] in their study.

2.1. Statistical analysis

Data were coded and entered using the statistical package SPSS, version 25 (IBM SPSS Statistics for Windows, Version 25.0.; IBM Corp., Armonk, New York). Data were summarized using mean and SD for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired $t$ test. For comparing categorical data, $\chi^2$ test was performed. Exact test was used instead when the expected frequency was less than 5. $P$ values less than 0.05 were considered as statistically significant.

3. Results

This study included 61 patients with a confirmed diagnosis of COVID-19. Participants in this study were stratified into two groups:

Group A included 50 patients, comprising 32 males and 18 females, aged 21–56 years with a mean age of 34 years. Group B included 11 controls, comprising seven males and four females, aged 23–45 years with a mean age of 32 years.

The differences in age and sex between the two groups were found to be statistically insignificant ($P = 0.57$ and 0.3, respectively).
By use of the subjective assessment, smell disorders were confirmed in all patients in group A, with 33 (66%) cases exhibiting anosmia, 11 (22%) cases with parosmia, and six (12%) cases exhibiting hyposmia. A total of 32 (64%) patients with smell disorders had a NLR more than 3. It is worth noting that all patients with parosmia (n = 11) showed NLR more than 10 with a mean of 14.7. Compared with the olfaction-recovery subgroup, the olfaction-no-recovery subgroup showed higher levels of CRP, ESR, and serum ferritin after 3 months of diagnosis. The comparison of results of CRP and ferritin at 3 months interval between both subgroups within group A showed significant differences, favoring lower values in the olfaction-recovery subgroup (Table 2).

4. Discussion

To our knowledge, this study is the first to evaluate the role of APRs in COVID-19-related olfactory dysfunctions.

In the present study, we reported 61 COVID-19-positive patients confirmed with rRT-PCR test, who were divided into two groups.

Some studies have reported female or male predomination in the development of olfactory disorders associated with sex-related differences in the inflammatory reaction process in COVID-19-positive patients [9,15]. However, in this study, no significant association was detected between sex and olfactory dysfunction.

Smell disorders were confirmed in all patients in group A, with 33 (66%) patients exhibiting anosmia, 11 (22%) patients with parosmia, and six (12%) patients exhibiting hyposmia.

In this study, the levels of CRP, ESR, and NLR were reported to be significantly increased in group A at 0 interval compared with group B (P = 0.003, 0.001, and 0.04, respectively). In group A, 64% of patients had a NLR more than 3.

In group A, 43 (86%) patients experienced full recovery of smell based on the subjective assessment, whereas 14% did not recover after 3 months of diagnosis. Of the 43 patients, 32 (74.4%) patients recovered within 2 weeks, whereas the remaining (25.6%) recovered after the fifth week of the diagnosis.

After 3 months of diagnosis, CRP, ESR, serum ferritin, and NLR started decreasing in patients in group A who experienced complete recovery of smell disorders (olfaction-recovery subgroup). Compared with the olfaction-recovery subgroup, the olfaction-no-recovery subgroup showed higher levels of CRP, ESR, and serum ferritin after 3 months of diagnosis. The comparison of results of CRP and ferritin at 3 months interval between both subgroups within group A showed significant differences, favoring lower values in the olfaction-recovery subgroup (Table 2).

Table 1. The results of acute-phase reactants and neutrophil-to-lymphocyte ratio at 0 interval between both groups.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mean ± SD)</td>
<td>28.3 ± 39</td>
<td>6.3 ± 2.5</td>
<td>0.003**</td>
</tr>
<tr>
<td>ESR (mean ± SD)</td>
<td>39.7 ± 35.8</td>
<td>5.2 ± 2.6</td>
<td>0.001***</td>
</tr>
<tr>
<td>Ferritin (mean ± SD)</td>
<td>121.2 ± 90.9</td>
<td>102 ± 86</td>
<td>0.7**NS</td>
</tr>
<tr>
<td>NLR (mean ± SD)</td>
<td>4.4 ± 1.8</td>
<td>1.5 ± 0.6</td>
<td>0.04*</td>
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</tbody>
</table>

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NLR, neutrophil-to-lymphocyte ratio.

*Significant at the 0.05 probability level.
**Significant at the 0.01 probability level.
***Significant at the 0.001 probability level.
†NS, nonsignificant at the 0.05 probability level.

Anosmia has already been described in common coronavirus infections [16]. Previous studies revealed that sudden anosmia might be the sole presenting symptom of COVID-19-infected patients [17,18].

Moein et al. [19] studied smell dysfunction in the COVID-19-infected patients, and they found that 59
(98%) of the 60 patients experienced a sort of olfactory dysfunction. Of the 60 patients, 35 (58%) were either anosmic (15/60; 25%) or hyposmic (44/60; 73%). Bhatta et al. [20] studied 188 COVID-19-positive patients and reported that the smell disturbance was present in 60.6% (hyposmia 36.1%, anosmia 20.2%, and parosmia 4.2%). The current study classified the smell dysfunctions into anosmia (66%), parosmia (22%), and hyposmia (12%).

The present study demonstrated improvement in smell disorders by 86% at 3 months of follow-up. Overall, 74.4% of the recovered patients experienced improvement of olfactory disorders within 2 weeks. Our results came in accordance with a previous study, which showed that nearly 80% of patients experienced improvement in smell disorders within a few weeks of onset [18], but was in contrast to another study, which reported lower rates of smell recovery (23/58; 39.66%) [21].

The rapid improvement in the smell disorders over short period of time in COVID-19-infected patients suggests transient inflammatory response of the virus over the nasal epithelial cells and the sensory receptors.

CRP and ESR are not only systemic inflammatory markers but also mediators of inflammatory process. CRP and ESR were found to be significantly high in the early stage of the COVID-19 infection in previous studies, but their association with olfactory dysfunction has not been studied [22,23].

Few studies that examined the association between inflammatory markers and olfactory function — unrelated to COVID-19 — found increased levels of cytokine interleukin-6 in blood plasma of participants with olfactory disorders, which induces a variety of acute-phase proteins such as CRP [24,25]. Unfortunately, interleukin-6 has not been studied in our study.

Furthermore, in patients with advanced renal impairment, olfactory disorders have been linked to higher levels of the inflammatory marker CRP [26].

This study reported that CRP and ESR were found to be significantly higher upon presentation in group A compared with group B. However, the levels of CRP at 0 and 3-month intervals showed significant decline.

NLR has been recognized in a meta-analysis as a prognostic biomarker for patients with sepsis [27]. For COVID-19-infected patients, NLR has been reported to be an independent risk factor for severity of COVID-19 disease [28].

In this study, NLR had been found to be associated with the development of olfactory disorders in COVID-19-infected patients upon presentation. This association was found to be especially high among patients mainly presenting with parosmia.

Thorough literature search failed to reveal a scientific explanation for the association of NLR to the onset of olfactory dysfunction; however, stem cell apoptosis may explain the persistence of elevation of NLR to failure of the olfactory recovery [29].

There are limitations associated with performance of the present study. The numbers of patients and controls included in this study were relatively small. One of the limitations of this study was the lack of objective assessment for olfactory dysfunction, but these were intentionally avoided owing to the high risk of COVID-19 transmission, the international shortage of personal protective equipment, and lack of effective vaccines. Indeed, participants in this study underwent strict inclusion and exclusion criteria, which amplifies the importance of results of the present study. Despite the global deficiency of the PCR kits and the relatively high cost of the test early after the discovery of the disease, all patients in our study had their diagnosis and recovery confirmed using rT-PCR. Group A patients had olfactory dysfunction as their sole COVID-19 symptom, whereas group B patients were completely asymptomatic and the only driver for them to seek medical advice was the contact or exposure to COVID-19-infected patients. This may be explained by the relatively small number of

Table 2. The results of acute-phase reactants and neutrophil-to-lymphocyte ratio at 3-month interval between the olfactory recovered and non-recovered patients in group A.

<table>
<thead>
<tr>
<th></th>
<th>Olfactory-recovered patients (N = 43)</th>
<th>Nonolfactory-recovered patients (N = 7)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mean ± SD)</td>
<td>8.4 ± 12.3</td>
<td>16 ± 18.2</td>
<td>0.01**</td>
</tr>
<tr>
<td>ESR (mean ± SD)</td>
<td>8.8 ± 4.7</td>
<td>74 ± 19.5</td>
<td>0.6†NS</td>
</tr>
<tr>
<td>Ferritin (mean ± SD)</td>
<td>56 ± 43.9</td>
<td>299 ± 143.9</td>
<td>0.04*</td>
</tr>
<tr>
<td>NLR (mean ± SD)</td>
<td>1.4 ± 1.94</td>
<td>8.7 ± 16.1</td>
<td>0.6†NS</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NLR, neutrophil-to-lymphocyte ratio.

*Significant at the 0.05.
**Significant at the 0.01 probability level.
†NS, nonsignificant at the 0.05 probability level.
patients included in this study and discrepancy in the sample size between both groups.

Future research on a larger sample size and better distribution of patients among study groups are required to reveal the complex mechanisms relating APRs and NLR to smell dysfunction in COVID-19-infected patients.

5. Conclusion

Elevated levels of CRP, ESR, and NLR in patients with olfactory dysfunction upon presentation suggest that they may play a role in the initiation of this symptom. Moreover, the decreasing levels of CRP and ferritin over 3 months in the olfaction-recovery group within group A suggests that they may be associated with and may be used as predictors of recovery. APRs can be used as helpful tools to predict the development and recovery of olfactory disorders in COVID-19-infected patients.

Author contribution

A.A.N made substantial contributions to the data collection and manuscript writing and gave final approval of the manuscript version to be published. A.M.E. made substantial contributions to the conception or design of the manuscript and data collection.

Conflicts of interest

There are no conflicts of interest.

References