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The Relationship between headache and hiposmi-anosmi in Covid-19 patients

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Abstract

Objective: The aim of this study is to evaluate the relationship of olfactory disorder with headache and laboratory findings in COVID-19 patients admitted to the emergency room with hyposmia-anosmia. *Methods:* Sixty-three patients admitted to the emergency room and diagnosed as COVID-19 according to WHO guidelines were included in the study. Medical records, laboratory findings and radiological findings were examined and then phone calls were made for additional data. Sociodemographic characteristics and emergency room symptoms at the time of admission of all patients testing positive for COVID-19 were evaluated. Neurological problems were assessed under two categories: Headache and olfactory disorders. The severity of the headache was evaluated by visual analog scale (VAS) and the duration of headache and time taken for resolution was recorded. In addition, the duration of the hyposmia-anosmia and its improvement time, starting from the COVID-19 symptoms, was recorded. *Results:* Twenty four (38%) presented with hyposmia-anosmia symptoms at the emergency room, while 39 (62%) patients had no symptoms of hyposmia-anosmia. Thirty three (52.4%) had a headache. Headache incidence and headache improvement time (days) in COVID-19 patients with olfactory impairment were significantly higher than in COVID-19 patients without olfactory complaints (p=0.002, p= 0.019). In addition, there was a correlation between the mean hyposmia-anosmia improvement time and headache improvement time (days) in the group presenting with olfactory impairment (r=0.81, p=0.001).
Conclusion: Clinicians should be aware of the relationship between headache and olfactory impairment in COVID-19 patients.

Keywords: Headache, COVID-19, SARS-CoV-2, olfactory impairment

INTRODUCTION

The new coronavirus (COVID-19), which causes coronavirus disease, was first detected in Wuhan city, China in December 2019[1] and quickly spread to more than 200 countries.[2]

As of June 2020, there were 51 million COVID-19 positive patients and 1.2 million deaths worldwide. At the same time, there were 397,000 COVID-19 positive patients and 11,000 COVID-19-induced deaths in Turkey.[2]

The primary symptoms involve the respiratory and cardiac systems, but central nervous system (CNS) symptoms are also reported in the literature as case reports and case series.

Commonly reported symptoms such as headache and dizziness and subsequent loss of consciousness, encephalopathy and delirium are present. Additionally, reported complications are clinical manifestation such as stroke, Guillain-Barre syndrome, acute transverse myelitis, and acute encephalitis.[3] The most common symptom of the peripheral nervous system (PNS) is anosmia. In addition, taste and vision disorders, and neuralgia are also among the PNS symptoms.[4]

While many theories exist regarding the pathophysiology of neurological system involvement of COVID-19, the exact cause is not clearly known. However, one of the mechanisms

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described is the invasion of peripheral nerve terminals by COVID-19 and then entry into the CNS via synaptic pathways.[5]

The aim of this study was to evaluate the relationship of olfactory impairment with headache and laboratory findings in COVID-19 patients admitted to the emergency room with hyposmia-anosmia.

METHOD

The study was conducted with the permission of the Ministry of Health of the Republic of Turkey (2020-06-05T22_31_14) This study was conducted at Bolu Abant Izzet Baysal University Training and Research Hospital, which was designated as a pandemic hospital by the government between March 2020 and May 2020. Of the 89 patients admitted to our hospital and diagnosed as COVID-19 according to WHO guidelines, 63 patients were included in the study after application of exclusion and inclusion criteria.

A confirmed COVID-19 case was defined as a positive result in the throat swab specimen analysis made by real-time reverse-transcription PCR analysis or high-throughput sequencing. After collecting the throat swabs, the samples were placed into a tube containing virus preservation solution. An infection of SARS-CoV-2 was confirmed by the real-time reverse-transcription PCR assay using the SARS-CoV-2 nucleic acid detection kit. Patients older than eighteen and diagnosed as COVID-19 were included in the study. Suspected COVID-19 patients who underwent PCR analysis twice with negative results in both tests, patients admitted to intensive care, unconscious patients whose headache could not be assessed, patients who had previous olfactory impairment or dizziness symptoms, who had rhinorrhea or nasal congestion, and who had chronic daily headache according to the International Classification of Headache Disorders criteria were excluded from the study.

Data collection and study design

Medical records, laboratory findings and radiological findings were examined and then phone calls were made for additional data. Sociodemographic characteristics (age, gender) of all the COVID-19 positive patients, their presenting symptoms (cough, fever, hyposmia-anosmia, sore throat, diarrhea, abdominal pain, etc.), hematological and other biochemical parameters (hemoglobin, leukocyte, platelets, sedimentation, C-reactive protein, D-dimer, fibrinogen), CT images (thorax and brain if available) were evaluated.

All neurological findings were evaluated by the same neurologist. Neurological problems were assessed under two categories: CNS (headache) and PNS (olfactory disorders). Headaches presented by these patients were classified according to the third edition of the International Classification of Headache Disorders (ICHD-3).[6] Headaches were classified as being associated with COVID-19 if they fulfilled criteria A to C1 for 'Headache attributed to systemic viral infection' (9.2.2).[6] The phenotypes of headaches associated with COVID-19 headache were classified as follows: Migraine phenotype: Headaches that fulfilled criteria B to D for migraine without aura (1.1). Tension-type headache: Headaches that fulfilled criteria B to D for tension-type headache (2.1). Cough headache phenotype: Headaches that fulfilled criteria B to D for cough headache (4.1). Those headaches that were aggravated only after coughing were not classified as cough headache.[6] The severity of the headache was evaluated by visual analog scale (VAS) and the duration of headache were recorded. Improvement time of headache was assessed with 0-point VAS scores. In addition, the duration of the hyposmia-anosmia and its improvement time, starting from the COVID-19 symptoms, were recorded.

The patients were divided into sub-groups according to their symptoms on admission, which were: the patients with and without headaches, and the patients with and without hyposmia-anosmia.

Statistical analysis

The data were analyzed using SPSS (SPSS 24.0, SPSS Inc., Chicago, Illinois, US) statistics software. Continuous variables were expressed by mean±standard deviation (SD). The Kolmogorov-Smirnov test was used to test the normality of the distribution of continuous variables. Student t-test was used for the comparison of variables with a normal distribution. Pearson correlation analysis was used in the analysis of variables in the patient group. For continuous variables, differences between the two groups were evaluated using the Mann–Whitney U test when the assumption of normality was not met. $p<0.05$ was considered statistically significant.

RESULTS

Of the 63 COVID-19 positive patients who participated in the study, 24 (38%) had complaints

Table 1: The frequency of incipient headache, headache duration, mean headache improvement time, and mean VAS values in patients with COVID-19, and p-values between the subgroups with or without hyposmia-anosmia symptoms

	Hyposmia-anosmia group Mean±SD (%) (n=24)	**Non-hyposmia-anosmia group** Mean±SD (%) (n=39)	**Total** Mean±SD (n=63)	**P-value**
Headache	19 (79.2%)	14 (35.9%)	33 (52.4%)	**0,002***
Daily headache duration (hours)	5.5±2.9	5.7±3	5.6±2.9	0.81
VAS scores	5.6±2.7	5.1±2.7	5.3±2.7	0.51
Headache improvement time (VAS scores=0) (days)	5.7±1.7	4.02±2.3	5.1±2.1	0.019*

*p<0.05
VAS: Visual Analog Scale

of hyposmia-anosmia in the emergency room, while 39 (62%) patients had no hyposmia-anosmia symptoms. Forty patients (63%) were male and 23 (37%) were female. The mean age was 42.2±12.8 (min:19, max:72). There was no significant difference in terms of age and gender in both groups (p=0.27, p=0.63, respectively).

Thorax CT imaging was performed in all patients, and brain CT imaging was performed in sixteen patients due to headache. While all patients had thorax CT findings consistent with COVID-19 in the lung, no acute abnormalities were found in any of the patients who underwent brain CT examination.

Of the 63 patients, 33 (52.4%) had a headache. The headache was characteristically bilateral, and in the frontal and posterior regions of the head. Fifteen of the 63 patients (23.8%) presented with headache triggered by coughing. Of these, six only had cough headache, five also had a migraine phenotype, and four had a tension-type headache phenotype. Ten of the 63 patients (12.6%) presented with migraine like headache and 8 of the 63 patients presented with tension-type headache without exacerbation by coughing.

Nineteen (79.2%) of the patients presenting with the hyposmia-anosmia symptoms had a headache, while only 14 (35.9%) of the patients presenting with other complaints had a headache. The headache prevalence rate was significantly higher in the group presenting with hyposmia-anosmia, compared to the other group of patients with other symptoms (p=0.002).

Considering the patients with headache as a whole; the mean headache duration per day was 5.6±2.9 hours, the mean VAS value was 5.3±2.7 (min:2, max:9), and the mean headache improvement time was 5.1±2.1 (min:1, max:9) days. Headache improvement time was also significantly longer in patients with olfactory symptoms compared to patients presenting without olfactory symptoms (p=0.019). There was no significant difference in terms of mean headache duration or mean VAS values in both groups (p=0.81, p=0.51, respectively).

Table 1 shows the mean headache duration (hours), mean headache improvement time (days), and mean VAS values of the patients in both groups. In the hyposmia-anosmia group, 13 of the hyposmic patients had headache and the median VAS value was 4 (IQR:7.2-8.2). Six of the anosmic patients had headache and the median VAS value was 8 (IQR:7.2-8.2).

In terms of serum laboratory parameters, no significant relationship was found between the hyposmia-anosmia group and the group without hyposmia-anosmia. The mean values of the serum laboratory parameters of the patients, and the p values between the two groups are shown in Table 2. Moreover, there was no significant difference in laboratory parameters between the patients with and without headache in both groups (Table 3).

The mean improvement time of hyposmia-anosmia symptoms were found to be 5.2±1.9 (min:1, max:9) days in the . There was a statistically significant correlation between hyposmia-anosmia symptoms and headache improvement times (days) in patients with hyposmia-anosmia and headache. (r=0.81, p=0.001)

Table 2: Means values of the serum laboratory analyses in COVID-19 patients and the p values between subgroups with and without hyposmia-anosmia symptoms

Serum Parameter	Hyposmia-Anosmia group Mean±SD (n=24)	Non-hyposmia-Anosmia group Mean±SD (n=39)	Total Mean±SD (n=63)	P-value
Hemoglobin (g/L)	14.4±1.8	14.2±1.5	14.3±1.6	0.64
Leukocyte (μl/ml)	5045±1753	5281±1470	5191±1574	0.56
CRP (mg/L)	8.1±8.1	8.3±11.3	8.2±10.1	0.92
Sedimentation (mm/hour)	14.6±9	17.2±11.5	16.2±10.6	0.35
Platelet ($10^3/\mu$L)	232±57	223±57	226±56	0.55
Ferritin (ug/L)	109±76	121±115	117±102	0.65
D-Dimer (mg/L)	0.46±0.40	0.59±0.93	0.54±0.77	0.53

CRP: C Reactive Protein

DISCUSSION

In the present study, the headache incidence rate and the headache improvement time (days) in the COVID-19 patient group with olfactory impairment was significantly higher than the COVID-19 patients without olfactory impairment. In addition, there was a correlation between the mean hyposmia-anosmia improvement time and the headache improvement time (days) in the group presenting with olfactory impairment. However, there was no significant difference in terms of daily mean headache duration (hours) and headache intensity in both groups.

Although COVID-19 is often characterized by respiratory system symptoms, such as fever, sore throat, shortness of breath, and coughing, there are widely reported cases in the last three months admitted with atypical symptoms, such as abdominal pain, headache, diarrhea, smell and taste disorders, muscle skeletal pains, and skin lesions.[7]

Headaches are reported very frequently. It is also noted that headache is the most commonly reported neurological symptom. On the other hand, the characteristic properties and localization of the headache have not been specifically reported.

Although the pathophysiology of headache is not clearly known, many mechanisms have been suggested. The respiratory epithelium is the primary target of coronaviruses. The target receptor for binding to the cell and subsequent internalization is mediated by the angiotensin-

Table 3: Means values of the serum laboratory analyses in COVID-19 patients and the p values between subgroups with and without headache symptom

Serum Parameter	Headache group Mean±SD (n=33)	Non-headache group Mean±SD (n=30)	Total Mean±SD (n=63)	P-value
Hemoglobin (g/L)	14.4±1.8	14.2±1.5	14.3±1.6	0.62
Leukocyte (μl/ml)	5045±1753	5281±1470	5191±1574	0.77
CRP (mg/L)	10.5±11.3	5.8±8.1	8.2±10.1	0.068
Sedimentation (mm/hour)	18.5±10.4	13.6±10.4	16.2±10.6	0.065
Platelet ($10^3/\mu$L)	233±61	219±50	226±56	0.32
Ferritin (ug/L)	128±98	104±106	117±102	0.34
D-Dimer (mg/L)	0.56±0.78	0.52±0.77	0.54±0.77	0.85

CRP: C Reactive Protein

converting enzyme 2 receptor (ACE-2). ACE-2 is effective in the regulation of blood pressure and is also present in the nervous system. COVID-19 has been reported to lead to blood-brain barrier disruption due to endothelial dysfunction and results in neurological sequelae due to direct or indirect mechanisms.[8] In addition, COVID-19 leads to alveolar inflammation and edema. This can lead to hypoxia in CNS and can affect cerebral blood flow and intracranial pressure, leading to many neurological symptoms ranging from headache to coma.[9]

Immune mediated injury is often caused by the cytokine storms. Increased D-dimer levels have been found to be linked to poor prognosis, and a thrombotic tendency along with the septic shock and multi-organ failure is present in severe COVID-19 cases. Some authors have also reported that the incidence of neurological symptoms is higher in severe COVID-19 cases.[7] In the present study, there was no significant relationship between hyposmia-anosmia and headache and hematological parameters (acute phase reactants and D-Dimer). On the other hand, patients with systemic complications such as septic shock, multi-organ failure, and severe neurological complications such as stroke, intracerebral hemorrhage, and meningoencephalitis were not included in the study.

The frequency of headache observed in the present study was much higher than that reported in most COVID-19 studies (11%, 27%, 34%, 48%, 39% and 43%).[10-15] In the present study, the incidence of headache was 52%. This high incidence of headache in the study may be due to the more detailed and careful questioning of the neurological symptoms, along with the respiratory system symptoms.

As is known, viruses such as parainfluenza Epstein-Barr virus, and some coronaviruses cause inflammatory reaction in the nasal mucosa, leading to rhinorrhea and olfactory problems. In the last few months, however, clinicians around the world have reported that COVID-19 causes severe olfactory disorders, regardless of nasal congestion and rhinorrhea.[16] In the present study, olfactory impairment was present in 24 (38%) COVID-19 positive patients. The frequency of hyposmia/anosmia and hypogeusia/ageusia observed in the present study is in line with that reported in the literature.[3,17-19]

In literature, there are few studies investigating the association of headache and olfactory impairment in COVID-19 patients. In a study from Brazil, patients who reported hyposmia/anosmia and/or hypogeusia/ageusia experienced headache more frequently than those without these symptoms. Furthermore, the authors noted a close temporal relationship between these symptoms, mostly occurring at the beginning of the symptomatic phase of COVID-19.[16] Another study also found a higher frequency of headaches amongst those who had anosmia.[20] In this study, it was found that there was a correlation between olfactory impairment and high headache incidence (79.2%), and that there was a correlation between the mean improvement time of both neurological symptoms.

When the pathophysiological mechanisms of both symptoms were examined, it was reported that it may be due to the trigeminal and olfactory nerve terminal involvement in relation to the ACE-2 receptor involvement in the nasal epithelial cells, in the case of COVID-19, as in SARS-CoV and MERS- CoV viruses. On the other hand, while transmembrane ACE-2 receptor involvement was detected in the olfactory and the gustatory cranial nerve terminals, it has not yet been demonstrated in the trigeminal nerve terminal.[18,21-23] The authors believe that both symptoms may be due to a common mechanism secondary to virus invasion in epithelial cells in the nasal cavity, affecting the terminal branches of the cranial nerves.[21,22]

The retrospective design of the research is among the limitations of the present study. However, all medical records and phone calls were made by the same researcher and examined in an early stage. Second, the low number of patients is considered as another limitation of the present study. On the other hand, we did not include patients who tested negative on PCR but had abnormalities on their thorax CT scans. Third, since patients with severe neurological involvement were not included in the study, the relationship of anosmia with other severe neurological symptoms in patients with COVID-19 was not evaluated. Fourth, neuroimaging, cerebrospinal fluid tests or ophthalmoscopy were not performed to rule out other causes of secondary headaches such as meningitis, encephalitis, and cerebrovascular diseases, which may be complications of COVID-19.[24] However, these patients had no meningeal or focal signs, confusional state, or impaired level of consciousness, which makes these complications less likely.

In conclusion, COVID-19 primarily affects the respiratory and cardiovascular systems. Nonetheless, neurological involvement is not uncommon and can lead to severe complications if not detected and managed at an early stage.

Headache was the most common neurological symptom seen in this disease. As a result of the present study, the patients with anosmia or hyposmia reported more headaches, which occurred in close temporal relationship with these symptoms. Thus, further studies are needed to evaluate this relationship more thoroughly.

DISCLOSURE

Conflict of interest: None

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