Covid-19 and headache characteristics

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Abstract

Background & Objective: Studies have shown that the most common neurologic symptom in patients with COVID-19 is headache, which may even be the first and only symptom. This study aimed to determine headache characteristics such as frequency, duration and localization, as well as the relationship of systemic inflammation with headaches in patients with COVID-19. *Methods:* A total of 202 patients hospitalized for COVID-19, consisting of 101 patients with headaches and 101 patients with no headache, were included in the study. Demographic characteristics, symptoms, clinical findings, and laboratory results were evaluated. In the group with headaches, visual analog scale (VAS) scores, duration, severity, and localization of pain were recorded. *Results:* One hundred nineteen (58.9%) of the patients had no headache in their previous medical history, whereas 21.3% (43/202) had a migraine history. Most of the patients with headache experienced short-term attacks of moderate-severity headaches (47.1%) that were pressing in nature (59%), and generalized (32.4%). We divided our patients into two groups according to pain severity: one of patients with mild-to-moderate headache and one of those with severe headache.. Pain characteristics were compared between the groups, and it was observed that the pain duration was longer in the group with severe pain (p<0.001). When the groups with and without headaches were compared, no significant differences were found between the groups regarding inflammatory markers such as lymphocyte count, lactate dehydrogenase, C-reactive protein, ferritin, and D-dimer levels.
Conclusion: The headache in our patients with COVID-19 was mostly new-onset, of moderate severity, compressive in nature, and generalized. Inflammatory markers were unrelated to the presence and severity of the headaches.

Keywords: SARS-CoV-2; COVID-19; headache; headache characteristics

INTRODUCTION

The global spread of COVID-19 was declared a pandemic by the World Health Organization (WHO) on March 11th, 2020. Unknown aspects of COVID-19 are being identified in light of progressively increasing case reports and scientific studies.[1,2]

Even though the SARS-CoV-2 virus commonly targets the respiratory system, neurologic symptoms frequently accompany the clinical features. It has been reported that smell-taste disorders, diarrhea, and headaches were frequently observed in addition to respiratory system findings. Symptoms of the disease may involve the central nervous system (CNS) (headache, acute cerebrovascular disorder, dizziness, impairment of consciousness, and seizures), the peripheral nervous system (PNS) (ageusia-gustatory impairment, anosmia, acute neuropathic disorders), as well as the musculoskeletal system (fatigue, muscle pain). In their retrospective observational study in China, Mao *et al.* identified neurologic symptoms in 36.4% of 214 patients with COVID-19 and reported the incidence of headaches as 13.1%.[3] In a meta-analysis study involving 3,598 cases, the incidence of headaches was 12%.[4] An interview-based cross-sectional study conducted in Spain reported the incidence of headache as 70%.[5] Various studies have reported that headaches might be associated with high fever in COVID-19, and patients may even present with headache as the first and only symptom.[4,6,7] It was reported that neurologic symptoms were more frequently observed in patients in whom the respiratory system was severely involved, and patients who developed neurologic symptoms tended to be older individuals with comorbidities.[3]

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It is believed that trigeminovacular pathway activation and inflammation are the most common of the possible mechanisms involved in the development of headache in COVID-19.[8] Studies on patients with COVID-19 have shown that, among the inflammatory markers, changes in lymphocyte counts and increases in C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, and D-dimer levels may be related to the course of the disease.[4]

Because headache characteristics in COVID-19 have not been clarified, and studies have only mentioned headache frequency to date, we aimed to determine the headache characteristics of patients with COVID-19 such as frequency, duration, localization, and severity. We also sought to determine the relationship of inflammatory markers to headache characteristics.

METHOD

This study was a single-center retrospective study in which inpatients with confirmed COVID-19 between March 2020 and November 2020 and treated by neurologists were included. Two hundred two patients comprising 101 patients with symptoms of headache and 101 patients with no headache during their hospital admission were included in the study. All patients with COVID-19 in this study were diagnosed according to the WHO guidelines, which require a positive throat swab result for SARS-CoV-2 real-time reverse transcription-polymerase chain reaction (rRT-PCR). Patients with a negative PCR test, inconsistent headache symptoms, secondary headaches (e.g. hypertensive, traumatic), loss of consciousness and lateralized deficit on neurologic examination, with headaches attributable to different infections, with intracranial space-occupying lesions, or cerebrovascular events (infarct, hemorrhage), and individuals aged under 18 years were excluded from the study. One hundred one of 135 patients with COVID-19 and headache were included in the study when these criteria were applied. The International Classification of Headache Disorders 3rd Edition (ICHD-3) was used to classify current and previous headaches.[9,10]

The demographic characteristics, medical history, symptoms, clinical findings, and laboratory and imaging results of the patients in the hospital electronic medical records were retrospectively evaluated. The patients' symptoms at first admission were recorded. Visual analog scale (VAS) pain scores, and the characteristics, frequency, severity, and location of headache were noted. The headache was classified as 'mild' if it did not affect daily activities without other symptoms of COVID-19, 'moderate' if it partially interfered with daily activity, and 'severe' if it was too intense to allow daily activities. Headaches of less than 4 hours in duration were considered short duration, and those lasting for 4 hours or longer as of long duration. The lymphocyte count, CRP, LDH, and ferritin levels were noted. Approval of the Local Ethics Committee (Protocol No: 2021/030) and the Ministry of Health were obtained for this retrospective study.

Statistical analysis

The Shapiro-Wilk test was used to assess the normality of the distribution of continuous variables. The Mann-Whitney U test was used to compare non-normal numerical data between two groups. The Chi-square test was used for categorical variables. Multivariate binary logistic regression analysis was performed to adjust the impact of age differences between the groups. Mean ± standard deviation (mean ± SD), median, and interquartile ranges were given regarding descriptive statistics. Statistical analysis was performed using SPSS for Windows version 24.0, and p-values <0.05 were considered statistically significant.

RESULTS

The mean age of the patients included in the study was 61.06±15.12 years; 51.5% (104/202) were male and 48.5% (98/202) were female. Anosmia-ageusia was seen in 85/202 (42.1%) of patients, cough in 78/202 (38.6%), shortness of breath in 42/202 (20.8%), fever in 42/202 (20.8%), and myalgia was observed in 24/202 (11.9%). The demographic profile of the patients included in the study is presented in Table 1.

One hundred nineteen (58.9%) of the patients had no previous headache, whereas 21.3% (43/202) had migraine. Of the 101 patients with a headache on admission, the pain severity was mild in 25.5% (26/101), moderate in 47.1% (48/101), and severe in 27.5% (28/101). Just over half (53.5%) (54/101) of the patients with a headache had short episodes of less than 4 hours' duration, whereas in 46.5% (47/101) attacks lasted for 4 hours or longer. The location of headache was holocranial in 32.4% (33/101), frontal in 29.4% (30/101), and bitemporal in 27.5% (28/101) of the patients (Figure 1). The headache was pressing in nature in 59% (59/101) of the patients; 25% (25/101) described a throbbing-type headache (Figure 2).

Table 1: Clinical characteristics of the patients with COVID-19

Variables		Descriptive Statistics (n=202)	
		Mean±SD	Median [min-max]
Age (years)		61.06 ± 15.12	62.5 [19 -95]
		n	**%**
Sex	Male	104	51.5
	Female	98	48.5
Smoking history	Present	41	20.3
	Absent	161	79.7
Onset of complaints	Anosmia-ageusia	85	42.1
	Shortness of breath	78	38.6
	Fever	42	20.8
	Cough	42	20.8
	Myalgia	24	11.9
	Diarrhea	7	3.5
	Fatigue	4	2.0
	Chest pain	3	1.5
	Sore throat	2	1.0

SD: Standard deviation

It was recorded that 43/83 (51.8%) of the patients with a history of headache had a diagnosis of migraine and 40/83 (48.2%) had tension-type and other types of headaches. Fifty-one of 83 (61.4%) patients described new headaches different from their previous headaches, 24/83 (28.9%) had similar headaches, 8/83 (9.6%) did not experience headache during their illness, although they had a history of headache. The mean VAS score was 5.64 ± 1.43 (Table 2).

The median age of the group with headaches [59 (range, 68-47) years] was significantly lower than of the group with no headaches [65 (range, 74-57) years] (p<0.001). When the clinical characteristics of the patient groups with and without headaches were compared, anosmia-ageusia was statistically significantly more common in the group with headaches [62.4% (63/101)] (p<0.001). No significant differences were found between the two groups regarding the lymphocyte, LDH, CRP, ferritin, and D-dimer levels (p=0.288, p=0885, p=0.479, p=0.180, and p=0.298, respectively) (Table 3).

When patients with mild-moderate headaches were compared with those with severe headaches, it was observed that 21 of 28 (75%) patients with severe headaches had a longer duration of pain (p=0.001). No significant differences were found in the characteristics and location of headaches among these groups (p=0.285, p=0.511). No significant differences were found between the two groups regarding lymphocyte, LDH, CRP, ferritin, and D-dimer levels (p=0.790, p=0.828, p=0.467, p=0.521, and p=0.062, respectively) (Table 3).

DISCUSSION

New symptoms are added daily to the known neurologic symptoms due to central and PNS involvements in COVID-19 disease caused by SARS-CoV-2. Numerous studies have reported that the most common and sometimes the only neurologic symptom in COVID-19 is headache; however, information on the characteristics, frequency, and severity of this headache is still insufficient.

In this study, we evaluated the severity, frequency, and characteristics of headaches in patients hospitalized with COVID-19. When all patients were evaluated, 21.3% were determined to have a previous migraine diagnosis, and 58.9% had no previous headache history. Wan et al. reported an incidence of 33% in their study.[11] In the study conducted by Moro et al., headache was observed in 61.9% of patients.[12]

Trigeminovascular pathway activation has been considered the most common mechanism
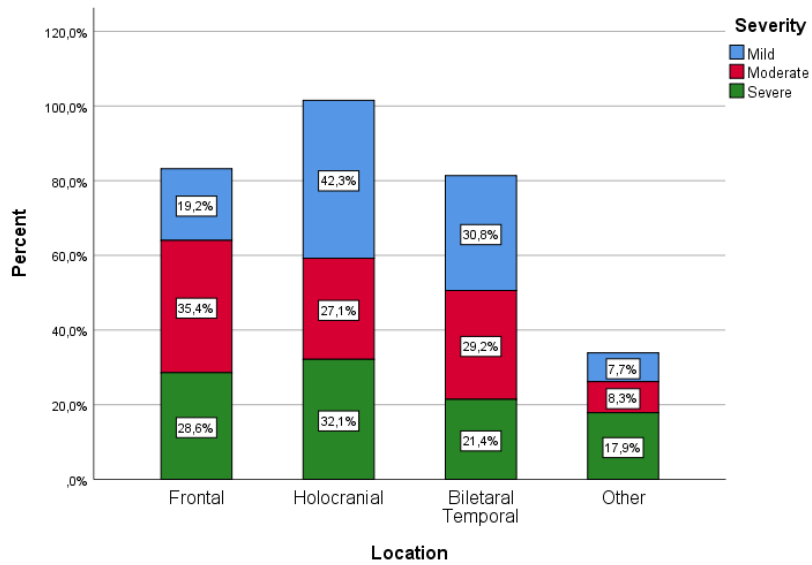
Figure 1. Localization of headache in patients with COVID-19.

responsible for headaches. Abnormal regulation due to over-expression of angiotensin-converting enzyme 2 (ACE2) (vasoconstriction, oxidative stress, and free radical formation) and inflammation in endothelial cells may play roles in trigeminovascular activation, leading to headaches. Regarding the pathogenesis, it has been suggested that the virus can trigger inflammation and headaches with secondary nociceptive stimulation, and thus steroid therapy might be beneficial. Also, nitric oxide and calcitonin gene-related peptide (CGRP) release due to hypoxia in patients may cause headaches by spreading cortical depression and disruption of the blood-brain barrier. Cerebrovascular events and sinus thromboses occurring secondary to thrombotic events may also present with headaches. Loss of appetite and dehydration due to diarrhea may
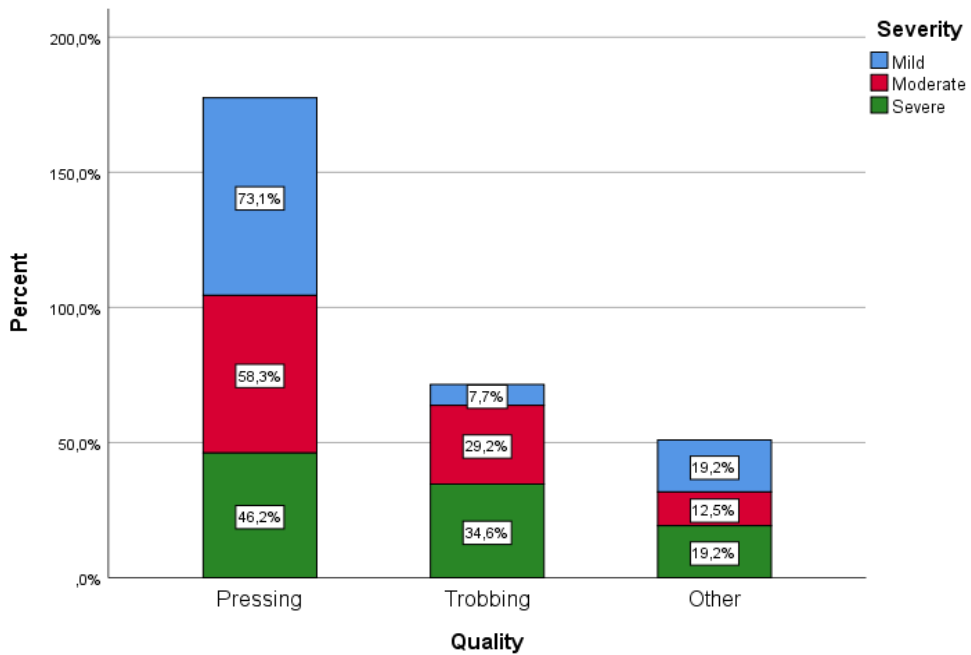

Figure 2. Pain characteristics in patients with COVID-19.

Table 2: Characteristics of Headache

		n	%
Headache	Present	101	50.0
	Absent	101	50.0
Pain severity	Mild	26	25.5
	Moderate	48	47.1
	Severe	28	27.5
Pain frequency	Short-term attacks, <4hrs	54	53.5
	Long-term attacks, ≥4hrs	47	46.5
Pain characteristics	Compressive	59	59.0
	Throbbing	25	25.0
	Other	16	16.0
Pain localization	Frontal	30	29.4
	Holocranial	33	32.4
	Bilateral temporal	28	27.5
	Other	11	10.8
Previous History of headache	Absent	119	58.9
	Migraine	43	21.3
	Another headache type	40	19.8
Headache character during COVID-19 period in patients with a history of headache	Absent	8	9.6
	New and different headache	51	61.4
	Old pain, similar headache	24	28.9
VAS (n=101)	5.64 ± 1.43	6 [3-9]	VAS (n=101)

Table 3: Comparison between COVID-19 patients with and without headaches

		Headache (n =101)	No headache (n=101)	P	$P_{adjusted}$
		n (%)	n (%)		
Sex	Male	49 (48.5)	55 (54.5)	0.398	0.339
Female		52 (51.5)	46 (45.5)		
Smoking history		22 (21.8)	19 (18.8)	0.600	0.230
Anosmia-ageusia		63 (62.4)	22 (21.8)	0.001*	0.001*
		Median [25-75%]	**Median [25-75%]**	**P**	$P_{adjusted}$
Age		59 [68-47]	65 [74-57]	0.001*	
Lymphocyte ×10³/uL		1.29 [1.6-0.92]	1.19 [1.6-0.99]	0.769	0.288
Lactate dehydrogenase U/L		270 [340-221]	287 [330-243]	0.404	0.885
C-reactive protein, mg/L		52 [86.9-19]	57.3 [109-21]	0.414	0.479
Ferritin, ng/mL		178 [316-84.5]	182 [367-115.3]	0.171	0.180
D-dimer, ng/mL)		0.36 [0.67-0.22]	0.39 [0.85-0.22]	0.296	0.298

*Significant at 0.05 level; Chi-square test for categorical data, Mann-Whitney U test for numerical data. $P_{adjusted:}$ Adjusted by age; Binary logistic regression analysis.

be partially responsible for headaches during the illness.[8,13,14]

Our study determined that the mean age of patients with headache was lower than that of the group without headache (p=0.001). It may be accounted for by a stronger immune response in the young. This finding needs to be clarified because no similar finding regarding the effect of age was found in previous studies.

Even though primary headaches, particularly migraines, are more common in females, it was reported that headache with COVID-19 is more frequent in males[15,16], possibly because of a higher incidence of atherosclerosis and hypertension. Female hormonal factors and the protective role of ACE-2 on the X chromosome may perhaps also explain this result, which needs to be clarified.[15] In our study, no statistically significant gender difference was present.

The virus's entry to the CNS through retrograde axonal transport and the direct invasion of the trigeminal nerve has been suggested to play significant roles in the etiology of headache, anosmia, and ageusia in patients with COVID-19. The association of headache with anosmia-ageusia has been linked to this pathophysiologic basis. Anosmia and ageusia are the most common symptoms of PNS involvement in patients with COVID-19. In this study, when the patient groups with and without headache were compared, it was determined that the incidence of anosmia-ageusia was significantly higher in the headache

Table 4: Comparison between patients with severe and mild-moderate headache

	Mild+moderate (n=74)	Severe (n=28)	P
Variables	n (%)	n (%)	
Sex			0.747
Male	37 (50)	13 (46.4)	
Female	37 (50)	15 (53.6)	
Smoking history	19 (25.7)	4 (14.3)	0.219
Anosmia-Ageusia	48 (64.9)	16 (57.1)	0.472
Pain frequency			0.001*
Short-term pain attacks, < 4hrs	47 (64.4)	7 (25)	
Long-term pain attacks, ≥ 4hrs	26 (35.6)	21 (75)	
Pain characteristics			0.285
Compressive	47 (63.5)	12 (46.2)	
Throbbing	16 (21.6)	9 (34.6)	
Other	11 (14.9)	5 (19.2)	
Pain localization			0.511
Frontal	22 (29.7)	8 (28.6)	
Holocranial	24 (32.4)	9 (32.1)	
Bilateral temporal	22 (29.7)	6 (21.4)	
Other	6 (8.1)	5 (17.9)	
	Mild+moderate (n=74)	Severe (n=28)	
	Median [25-75%]	Median [25-75%]	P
Age	59 [66-47]	62.5 [70.5-53]	0.162
Lymphocyte x10^3 /uL	1.3 [1.62-0.97]	1.3 [1.71-0.77]	0.790
Lactate Dehydrogenase, U/L	268 [340-227]	278 [341-187.5]	0.828
C-reactive protein, mg/L	52 [80.8-20]	50 [160-14.3]	0.467
Ferritin, ng/mL	163.1 [296-84.5]	214.2 [390.9-62.65]	0.521
D-dimer ng/ml	0.33 [0.62-0.19]	0.41 [0.82-0.31]	0.062

*Significant at 0.05 level; Chi-square test for categorical data, Mann-Whitney U test for numerical data.

group (63%, p<0.001). Previous case series have frequently related headaches to anosmia-ageusia.[13,17,18] In this study, consistent with the literature, anosmia-ageusia was more common in patients with headaches.

According to the observations of Bolay *et al.*, COVID-19–associated headache was usually new-onset, moderate to severe in intensity, bilateral temporal, pressing, or throbbing.[13] Our study found that the majority of patients had moderate severity (47.1%), pressing-type (59%), short-term generalized headache attacks (32.4%) (Figures 1 and 2). The median VAS pain intensity score was determined as 6 (range, 3-9), and 58.9% of the patients were determined to have no previous history of headaches. In the study by Caronna *et al*. in which 130 patients were evaluated, it was observed that 50.6% of the headaches were of moderate severity, 47.4% were frontally located, and 70.1% had features of a pressing-type headache.[19] A cross-sectional study on 172 patients reported that headache started together with COVID-19 (57%), spreading all over the head (52.9%), with characteristics of pressing-type headache (40.7%), and a VAS score of 7.[20]

In our study, 68 (67.3%) of 101 patients with headache did not have a history of headache, and these patients described new-onset headache with COVID-19. When the patients with a history of headache were evaluated, it was found that 43 of 83 patients had a history of migraine and 40 had tension-type and other types of pain. Fifty-one (61.4%) of the patients with a history of headache described a new pain with a different character from their old pain, and 24 (28.9%) described similar pain. These findings suggest that COVID-19 causes a new headache with specific clinical features, and it can often cause a new and different type of headache in patients with a history of headache. In a previous study that evaluated the coexistence of COVID-19 and headache, it was reported that 79.5% (89/112) of the patients who had headaches before and during their illness reported that the latter had different characteristics from the former. In 50% (56/112) the headache had completely different features, while 29.5% (33/112) reported partially similar features.[15] These findings suggest that COVID-19 causes a new headache with specific clinical features, and it can often cause a new and different type of headache in patients with a history of headache.

No statistically significant difference was observed with respect to laboratory parameters between the groups with and without headache, and between the groups with mild-moderate and severe headaches.

It has been reported that high CRP values can reduce the pain threshold, and that inflammation may cause various types of headaches. However, our study finds that CRP was unrelated to the presence or absence of headache in COVID-19.[21] It has been reported that lymphocyte, D-dimer, LDH, and ferritin play a role in pro-inflammatory and anti-inflammatory processes. They are associated with acute respiratory syndrome (ARDS) development, need for intensive care, and mortality in patients with COVID-19.[22] However, our study also finds no differences between the groups with and without headache in these parameters. Other studies similarly have not found an increase in inflammatory markers (CRP, lymphocyte, D-dimer, and ferritin values) in headache associated with COVID-19.[19,20] These results suggest that inflammatory markers are not of clinical value in diagnosis and follow-up of patients with COVID-19 and headache.

When we compared the groups with mild-moderate and severe headaches, we observed that headaches lasted longer in the group with severe headaches, but that there were no significant inter-group differences in headache location and characteristics.

Our study has various limitations. This study was planned as a single-center study involving patients with clinical follow-up under pandemic conditions. Cranial imaging could only be performed in a limited number of patients due to the pandemic. Also, further specific evaluations such as CSF analysis, advanced blood investigations, and electrophysiologic assessments of these patients were not performed. We could not retrieve sufficient data to contribute to the literature regarding the patients' treatment response and the efficacy of analgesics and steroid treatments because the study was a retrospective review. We could not obtain data on the duration of present headaches because follow-up could not be performed after discharge from the hospital.

For this reason, further assessments in more extensive case series are required to identify the duration of COVID-19 headache, determine the acute and prophylactic treatment options in this period, plan treatment, and construct treatment algorithms using effective treatment options.

In conclusion, we found that the COVID-19–related headache was most commonly a new-onset, moderately severe holocephalic headache with a pressing-type character. Inflammatory markers did

not differ between the groups with and without pain, or according to the severity of pain. More comprehensive, multi-center, advanced studies with larger sample sizes, including autopsy studies, are required for definitive criteria on this subject.

DISCLOSURE

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