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Headache Characteristics of Patients with COVID-19 in Turkey: Is COVID-19 Infection a Trigger for Migraine Headache?

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ABSTRACT

Introduction: Headache is a common symptom in patients with Coronavirus-19 infection (COVID-19). In this research, we aim to assess the frequency, characteristics, and response to treatment of headache in patients with COVID-19 and its correlation with psychosocial features in Turkey.

Methods: To describe the clinical features of headache in COVID-19 positive individuals. Patients were evaluated and followed up with face-to-face visits in a tertiary hospital during the pandemic period.

Results: One hundred and seventeen of 150 patients (78%) had a headache diagnosed before and during the pandemic, 62 of 150 (41.3%) had a new type of headache. No significant differences were observed in terms of demographics, Beck Depression Score, Beck Anxiety Score, and quality of life scales (QOLS) between patients with and without headache (p>0.05). The most common triggering factor for headache was stress and fatigue in 59% (n=69), while the second most common (32.4%, n=38) was COVID-19 infection. 46.5% of the patients reported that the severity and frequency of their current headaches increased after the COVID-19 infection. Among new-onset headaches, the social functionality and pain score subgroups of the QOLS form were significantly lower in housewives and unemployed patients compared to the working group (p=0.018; p=0.039 respectively). Twelve of 117 patients had a mild to moderate, throbbing headache in the temporoparietal region, which did not fulfill the International Classification of Headache Disorders diagnosis criteria, but showed as a common feature among COVID-19 patients. Nineteen of 62 patients (30.9%) had a newly diagnosed migraine syndrome.

Conclusion: The diagnosis incidence of migraine in patients with COVID-19 disease being more than other headaches types may suggest the existence of a common pathway in possible immune mechanisms.

Keywords: Migraine disorders, patients with COVID-19, primary headache disorders, quality of life score

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INTRODUCTION

Coronavirus infection (COVID-19) symptoms mainly arise from the respiratory system, but in recent publications, it has been increasingly shown that symptoms of the central nervous system (CNS) also play a major role in the course of disease. Headache is the most frequent central nervous symptom in recent researches. The pathophysiological explanation of CNS involvement has not yet been clearly understood, and efforts have been made to explain the direct invasion to the CNS, the autoimmune pathways, and the consequences of cardiovascular and metabolic disturbances with primary involvement. Mortality rates are increasing with the broader spread of the disease. World statistics indicate that the mortality rate varies among countries, but the empirical values vary between 0.1 to 5.1 percent (1). In an analysis performed at Lütfi Kırdar City Hospital, the value was estimated to be 1.9% (2).

Headache is a common symptom of COVID-19 and may be experienced by up to 40% of the patients (3). Headache frequency has been reviewed in COVID-19 studies in the literature by Lippi et al. and the analysis of the data from eleven studies found that headache frequency ranged between 6.5 and 40 percent. In the COVID-19 cases, the pathogenesis of the headache is not entirely understood (4). However, it is believed that three different mechanisms may play a role in headaches in patients with COVID-19. It is suggested that headaches are associated with proinflammatory mediators and cytokines released because of the inflammation or can be caused directly by a viral invasion of the trigeminal nervous system through the nasal cavity. Another mechanism of headache may be of trigeminovascular origin by the involvement of endothelial cells, which are rich in angiotensin-converting enzyme-2 (ACE-2) expression (5,6).

It can be difficult to treat and follow patients dealing with the main complaint of headache during a pandemic period. Primary headaches may increase, especially in times of stress, with sleep disorders and malnutrition. While paracetamol and triptans are the most reliable prescription medication used to treat recurrence, more evidence for the use of ACE-2 inhibitors is needed. Discussions are still ongoing surrounding the use of primary headache prophylaxis of ACE antagonists

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Highlights

- **Headache increased in 46.5% of patients after covid-19**
- **41.3% of the patients with COVID-19 infection had a new type of headache.**
- **The most common new diagnosis in COVID-19 patients was migraine (30.9%)**
- **A common type of headache is not fit any of the classifications was observed in COVID-19 patients**
- **The quality of life scale was similar in patients with and without headache.**

or angiotensin receptor blockers as COVID-19 works via the ACE receptors (7).

In this research, we aimed to investigate the presence of headaches, headache characteristics, the frequency of patients with COVID-19 during the time of a pandemic, old and new headache diagnosis, responses to treatment of these headaches and the correlation of these psychosocial causes, and its impact on quality of life in Turkey.

METHODS

Participants and Study Design

We performed a descriptive, cross-sectional, observational study of the clinical characteristics of headache in patients with COVID-19 during pandemic between April 2020 and February 2021. In March 2020, the pandemic started in our country, and to follow those cases a specialized clinic in our neurology outpatient department was opened. Patient appointments were made face to face in the mentioned neurology clinic, and after diagnosis, we have planned final examinations (at 2–5 weeks after diagnosis). At that time, we advised the patients to note a new headache or changes in their headache characteristics and record the medications they were using.

A questionnaire based on patient complaints was then prepared by the researchers. This form included the presence of new headaches during the pandemic; old headaches before COVID-19 diagnosis and during the time of illness, the characteristics of all headaches (such as duration, frequency, location, the severity of headaches, response to treatment), and sociodemographic features of all patients. In addition, psychosocial causes were explored using Beck Depression and Beck Anxiety forms (8,9). SF-36 life quality scale has been applied to assess the effects on the quality of life of old and new headaches (10).

In this study, patients were split into two groups as with and without headaches. In the headache group that was followed, those with recent headaches and those with past headaches were compared. In addition, the old and new characteristics of the headaches were compared between the groups during the pandemic period.

Previous headaches presented by these patients were classified according to the third edition of the International Classification of Headache Disorders (ICHD-3) (11).

Inclusion and Exclusion Criteria

In our country's health system, only patients with polymerase chain reaction (PCR) positivity can be diagnosed with COVID-19. After the Ethics Committee approval (17.04.2020/520), patients over 18 years of age who have been diagnosed with COVID-19 on the basis of our country's COVID-19 disease diagnostic criteria (both symptomatic and asymptomatic patients with the condition of displaying COVID-19 seropositivity) have been included in the research on a voluntary basis. All patients were examined by a neurologist and cranial imaging (brain magnetic resonance imaging) was performed for all patients.

Patients under the age of 18, patients with a learning disability, who might have trouble reading the questionnaire, those with a severe medical condition, and those with a diagnosis of other infections except COVID-19, patients with space-occupying lesions that may cause a headache on cranial MRI, other infectious causes such as meningitis, encephalitis, and those diagnosed with stroke were excluded from this study.

Statistical Analysis

Descriptive statistics for continuous variables were given as mean and standard deviation. Frequency and percentage distribution were used for categorical variables. Shapiro-Wilk test was used as a normality test. Independent samples t-test for normally distributed variables and Mann-Whitney U test for abnormally distributed variables were used to compare two independent groups.

The Chi-square test or Fisher's exact test was used to compare categorical variables. Statistical analyses were performed using IBM SPSS (Statistical Package of Social Science) Version 18 and $p<0.05$ was accepted as the statistical significance level.

RESULTS

One hundred fifty (n: 150) patients with COVID-19 participated in the study, 82 of whom were female (54.7%). The average age was 38.96±13.21 (min-max: 18–71years). Women had an average age of 36.70±12.60 (min-max: 18–65yrs), while men had an average age of 41.69±13.49 (min-max: 18–71yrs), and women were younger than men statistically (p=0.021). Thirty percent had a high school diploma; 27.3% had a bachelor's degree or higher.

There were 118 self-employed people and 21 housewives. 20.7% (n: 31) were smokers and 7.3% used alcohol (n: 11). The average body mass index (BMI) was 27.28, and there was no gender difference. In the medical history of 63 individuals, there was a prior diagnosis of headache (42%).

Concerning other demographic variables, there was no statistically important difference in gender (p>0.05) and quality-of-life scale (total score and subgroups scores of SF-36) ratings (gender, BMI, occupation, personal and family history, alcohol use-smoking (p>0.05).

The mean Beck depression score was calculated as 10.21±8.9 (min-max: 0–31) and the average anxiety score as 13.93±12.3. Females scored significantly higher than males on both scores (p=0.001, p=0.00, respectively).

In our study, of the 150 patients with COVID-19 infection which were evaluated, 117 (78%) had a headache. The demographic and clinical information for the group with headaches is summarized in Table 1. No statistically significant difference was found regarding Beck Depression Score, Beck anxiety score, quality of life scales, and family history or background of patient groups with (n: 117) and without headache (n: 33) (p>0.05).

Among the headache group, the most common triggering factor was stress and fatigue with 59% (n: 69), while the second was having COVID-19 infection (32.4%, n: 38) [patients in this group reported either increased frequency/duration of existing headaches or experienced a

Table 1. Characteristics of headache during a pandemic

		Patients with headache during pandemic (n: 117)
Age year, mean (min-max)		37.47 (18–71)
Sex (n) (male/female)		50/67
Headache duration month		58.8±14.09
Headache characteristics		
	Pulsating n (%)	48 (41%)
	Pressing n (%)	21 (17.9%)
	Burning n (%)	6 (5.12%)
	Numbness/tingling n (%)	35 (29.9%)
	Stabbing n (%)	7 (5.98%)
Working status		
	Housewife/unemployed n (%)	32 (21.3%)
	Employed n (%)	118 (78.7%)
Headache progress		
	No change (n) (%)	35 (29.9%)
	Frequency increased (n) (%)	32 (27.3%)
	Intensity increased (n) (%)	26 (22.2%)
	Frequency decreased (n) (%)	14 (11.9%)
	Intensity decreased (n) (%)	10 (8.5%)
Type of analgesic		
	Paracetamol (n) (%)	64 (54.7%)
	Paracetamol+kafein (n) (%)	14 (11.9%)
	Flurbiprofen (n) (%)	10 (8.5%)
	Dexketoprofen (n) (%)	12 (10.2%)
	Diclofenac sodium/potasium (n) (%)	7 (5.98%)
	Others (n) (%)	10 (8.5%)

new headache during COVID-19 infection], with the third one being sleep problems (8.5%, n: 10). Headaches lasting over 12 hours were reported by 30.7% (36 out of 117 participants) of COVID-19 infected patients. Furthermore, 58 of 117 patients reported that their headache frequency was higher compared to the pre-pandemic levels and that their headache severity got worse during the pandemic (Table 1).

The presence of headaches in patients with COVID-19 during the pandemic period did not affect Beck Depression, Beck Anxiety, SF-36 quality of life scores statistically. However, the frequency and the severity of headaches increased in 65% of the patients (Table 1).

New-onset headaches were detected in 62 people (41.3%). When the headache characteristics of the patients were evaluated face-to-face within our study and questionnaire, it was found that the most common diagnosis was migraine (n: 19). Other diagnoses were nine patients with tension-type headache, six patients with headache secondary to hypertension, and two patients with cluster headache, respectively (Table 2).

Of the 62 patients with new-onset headaches, the social functionality and pain score subgroups of the SF-36 form were significantly lower in housewives and unemployed patients than the working group (p=0.018; p=0.039, respectively). There was no significant relationship between the presence of new-onset headache and beck depression, beck anxiety, and SF-36 scores (p>0.05). No statistically significant result was obtained regarding the presence of new headache diagnosis and demographic data (p>0.05) (Table 3).

Two findings were found to be remarkable in the newly diagnosed headache group. The first one was that 12 people had a mild to moderate throbbing headache in the temporoparietal region of the head, back of the ear, which did not meet the diagnostic criteria but showed a common feature among the patients interestingly. The second finding which was that the most common symptom accompanying headache in both patient groups (patients with known headache diagnosis and patients with new-onset headache) was photosensitivity and nausea during the period when they were diagnosed with COVID-19 positivity from the serum samples (Figure 1).

Of the 117 patients with headaches, 55 had at least one previous diagnosis (known headache). These were 8 migraine headaches, 10 tension-type headaches, one cluster headache and 36 were secondary headaches, respectively (Table 2). In face-to-face appointments, patients were questioned about headache changes before and after the pandemic and their characteristics during the period of illness. Generally, during the pandemic period, all patients had a throbbing suppressive headache, with 0–2 attacks per month for a maximum of 24 hours. In the period with COVID-19 positivity, 46.5% of the patients reported that the severity and frequency of their current headaches increased, while 34.3% reported that there was no change in their headache characteristics. 10% did not answer this question. There was no statistically significant difference in headache character traits before and during the pandemic (p>0.05)

Between new-onset and previously known headache patients, there were no statistically significant differences in demographics, Beck Anxiety / Beck Depression scores, or SF-36 scores except having a family history of migraine headache. In patients with a family history of migraine, being newly diagnosed with migraine during the pandemic was significantly higher than other headache diagnoses (p<0.05). The most common diagnosis of new headache in patients with COVID-19 was migraine (p<0.05). Pulsating quality was more pronounced for both

Table 2. Headache types patients with COVID-19

Headache types	Known headache before pandemic (n: 55)	New onset headache during pandemic (n: 62)	Patients without headache during pandemic (n: 33)
Migraine n (%)	8 (14.5)	19 (30.6)	0 (0)
Tension type headache n (%)	10 (18.1)	9 (14.5)	0 (0)
Cluster type headache n (%)	1 (1.8)	2 (3.2)	0 (0)
New daily persistent headache n (%)	2 (3.6)	1 (1.6)	0 (0)
Secondary type headache (sinusitis, hypertension etc.) n (%)	34 (61.8)	31 (50)	0 (0)
Patients without headache	0 (0)	0 (0)	33 (100)

Table 3. Comparison of test scores of two groups with and without new onset headache

Tests	Patients with new onset headache (n: 62)	Patients without new onset headache (n: 88)	p value
Beck Depression (mean ± SD)	10.10±9.51	10.30±8.51	0.894
Beck Anxiety (mean ± SD)	14.73±13.47	13.38±11.62	0.524
Physical function (mean ± SD)	75.82±24.82	77.85±24.55	0.622
Physical Role difficulty (mean ± SD)	54.92±39.48	47.90±40.82	0.297
Emotional role difficulty (mean ± SD)	53.57±35.64	54.93±34.30	0.815
Energy/vitality (mean ± SD)	48.51±20.79	55.44±47.66	0.288
Mental health (mean ± SD)	63.01±21.81	62.84±20.20	0.96
Social Functionality (mean ± SD)	60.37±29.24	62.45±26.21	0.649
Pain (mean ± SD)	52.46±28.98	52.30±29.17	0.973
General health (mean ± SD)	54.92±20.40	58.07±18.88	0.334
Health change (mean ± SD)	43.46±25.36	50.24±24.70	0.105

groups, including known headache (89%) and new-onset headache (80%) diagnosis.

66.6% of the patients preferred paracetamol treatment (Table 1). A decrease in pain intensity and/or frequency was observed in 83 of 117 patients with symptomatic treatment. However, 74% (20/27) of migraine patients did not respond to treatments involving paracetamol. It was noted that these patients preferred other analgesic treatments.

DISCUSSION

COVID-19 infection is known to affect both the central and peripheral nervous systems. It is believed that causing mitochondrial anaerobic respiration after hypoxic injury results in cerebral vasodilation, slowing of blood flow, and causing ischemia with rising proinflammatory cytokines. However, the mechanisms of injury to the nervous system by SARS-Cov-2 are not yet fully understood. In the literature, the rate of CNS involvement has been reported to be 36.4%. Among patients with COVID-19, this infection generally causes headache complaints in the central nervous system (12). Thus, the most frequent neurological symptom, with a prevalence of 52.1 percent, is headache (13). However, this ratio changes due to the clinical spectrum width and population difference. A study from Brazil included 72 patients with COVID-19 where 36% had a new-onset headache. In a review by Lippi et al., headache rates were examined in the studies on COVID-19 in the literature, and the headache frequency ranged from 6.5% to 40% with the analysis of the data from 11 studies (4). In a large cohort study by Uygun et al. in Turkey, of 262 patients who were COVID-19 positive, it was observed that 33.2% had a new headache, while 44.3% had a previous diagnosis of headache.[14] In our study, new-onset headaches were detected in 62 people (41.3%). 78% of patients with COVID -19 positivity had a primary or secondary headache, wherein migraine (23.48%) was found to be most frequent among primary headache types. The difference between results can stem from the facts that there was no healthcare personnel in the study population, the research was conducted in a face-to-face environment under the observation of the researchers, and there were fewer patients compared to the research conducted with online forms in Turkey.

In the literature, headache characteristics of patients with COVID-19 were mentioned to be commonly localized and lateralized at the bilateral frontal or temporo-occipital area, to be throbbing and/or pressing in nature and not exceeding 72 hours (14–16). In one study, headache characteristics of the patients were listed as follows: 75% photophonophobia, 51% pulsative, 43% pressing, 53% severe pain, 94% bilateral, often in the frontal and temporoparietal regions with a

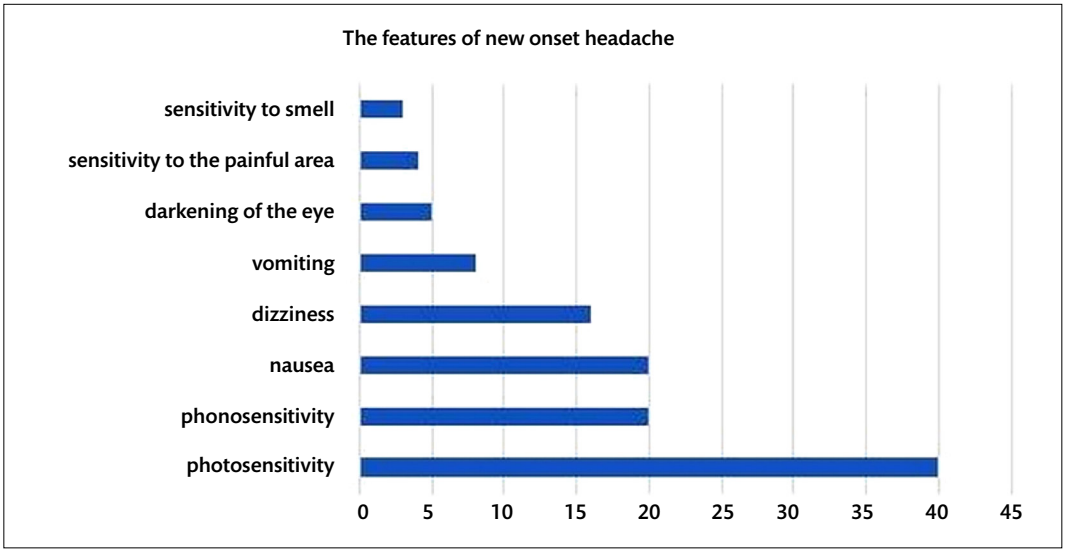

Figure 1. The features of new-onset headaches of patients with COVID-19.

duration of 1–2 days (15). The research from Turkey has shown nausea with 70.8%, photo-phonophobia with 63.9–67%, anosmia/ageusia with 74.5%, rhinorrhoea with 62.2% among their COVID-19 positive patients suffering from a headache (14). In a study conducted in Brazil, the percentage of COVID-19 infection-related headaches was reported to be 64.4% (15). In our results, patients with headache did not report any rhinorrhoea and anosmia/ageusia during the pandemic, and their headache characteristics were shown to be similar except being of a mild to moderate severity, having a shorter duration (headaches lasting over 12 hours were reported by 30.7% (36 out of 117 participants)) and being partially responsive to analgesic treatment. This difference may be due to several factors, such as the population participating in the study being active before the pandemic and being in quarantine and resting in the pandemic, needing less treatment, and not including any healthcare personnel in the study group.

The current study's findings were given as the most common stress factors, the second most common result of the COVID-19 virus, corresponding with subsequent research done in our country wherein the factors triggering pandemic headache were detailed. Similar characteristics were discovered in research conducted in various countries (14,16,17).

In a publication from Brazil, it was reported that those with a history of migraine (83%) or tension headache (50%) had a higher percentage of COVID-19-related headaches during the illness period (15). It was observed that they experienced migraine-like headaches on the first day of the disease. It was also reported in the same publication that tension-type headaches developed, but migraine-like pain was the primary complaint. Another recent research found that migraine-like headache frequency was more common than other primary headache types, including tension-type and cluster [Migraine 17.9%, tension-type headache 7.1%, cluster headache 0.9%] (14,16,17). Similarly, in our results, it was observed that the new diagnosis of migraine without aura, which met the diagnosis criteria for migraine after the disease, was significantly more common in our patient group with COVID-19 infection, followed by a new diagnosis of a tension headache without any significance.

To our knowledge, previous studies have examined the effects of the COVID-19 disease pandemic on migraine in Italian (18), Kuwaiti (19), Spanish (20) populations. They revealed that lockdown and its repercussions, such as changes in lifestyle choices, access to medicine, and being unable to attend in-person consultations, might harm the health of patients with migraine. In our study, no relationship was found concerning the presence of headache in beck anxiety beck depression and quality of life scales, and we realized that the patient group had the opportunity to rest during the quarantine period and that headache was not triggered due to a severe stress factor during the pandemic period. However, we observed that the diagnosis of migraine increased, especially with regard to primary headache diagnosis, and patients frequently experienced migraine-like attacks despite this situation. It has been reported in literature shared in the United States that the diagnosis of migraine increases in the further follow-up of patients with COVID-19 infection (20).

Of the 62 patients with new-onset headaches, the social functionality and pain score subgroups of the SF-36 form were significantly lower in housewives and unemployed patients than the working group (p=0.018; p=0.039, respectively). Primary headaches and COVID-19 related headaches reported during the pandemic era were shown to have no substantial impact on quality of life. This finding suggests that because of the epidemic, individuals are staying at home; thus they are not involved in stressful settings, such as work or traffic.

Except for migraine patients, more than half of the patients responded to analgesic treatments for headache. It is known that analgesics with dominant anti-inflammatory properties partially reduce migraine headaches (18,19). Due to the reservations about using these painkillers during the pandemic period, it was thought that patients mostly used paracetamol treatment and therefore migraine patients could not respond to headache treatment.

CONCLUSION

In our face-to-face and follow-up study, it was determined that patients with COVID-19 were most frequently newly-diagnosed with migraine, which made us think of possible common pathophysiological mechanisms for these two diseases. In addition, a common headache localization was noted, which could not be diagnosed with known headaches by ICHD criteria, but was frequently experienced during the active period of the COVID-19 disease.

Ethics Committee Approval: İstanbul Training and Reserach Hospital Ethics Committee approval (17.04.2020/520)

Informed Consent: Informed consent form was obtained from all participants.

Peer-review: Externally peer-reviewed.

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