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Patterns of COVID-19-related headache: A cross-sectional study

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ABSTRACT

Background: Headache is the most common COVID-19-related neurological symptom. We investigated the characteristics of COVID-19-related headache and their relationship with clinical severity in Kirsehir Province, Turkey.

Methods: This cross-sectional study prospectively enrolled 226 COVID-19-positive patients who developed headache during acute infection. Demographic data, headache characteristics, and infection symptoms were recorded. The clinical severity of COVID-19 was documented in each participant.

Result: New-onset COVID-19-related headaches lasting 4 days were reported in 164 patients (72.5%); these were mostly bilaterally or localized to the forehead (58.4%), pulsating (42.5%), moderate to severe intensity (30.1%), with a partial response to paracetamol (23.5%). The other 62 patients (27.4%) reported headaches before COVID-19. Their COVID-related headaches were fiery type (p = 0.025), of very severe intensity (p = 0.008), had a holocranial distribution (p = 0.004), and were less response to paracetamol (p = 0.003); the headaches were significantly more frequent after COVID-19 than before COVID-19. Older age, high body mass index, and low education level were significantly higher in the severe group (all p < 0.001). Female sex (p = 0.019) and being a healthcare worker (p < 0.001) were significantly more frequent in mild cases.

Conclusions: Bilateral, prolonged, moderate to severe headaches that were analgesic resistant are more frequent in patients with COVID-19 infection. Further study should examine whether the headache characteristics distinguish COVID-19-related headaches from other types, particularly in asymptomatic subjects.

1. Introduction

COVID-19 infection is a potentially fatal disease, primarily affecting the respiratory system, although central and peripheral nervous system involvement also occurs [1–3]. The SARS-CoV-2 virus enters cells by binding to the angiotensin converting enzyme 2 (ACE2) receptor found in many tissues, including the nervous system [4–8]. Possible mechanisms for central nervous system involvement include the direct effects of the virus via peripheral cranial nerves or hematogenous spread to infect endothelial cells in the blood–brain barrier and the indirect effects of the increased cytokines due to widespread systemic inflammation and the immune response or hypoxia [9–12]. The combination of direct and indirect processes can lead to brain dysfunction [13].

Neurological symptoms occur in 57.4% of COVID-19 patients [14]. One of the most common neurological symptoms is headache (14.1%) [14]. Three mechanisms have been proposed for these headaches. The first is direct entry by SARS-CoV-2 into trigeminal nerve endings in the nasal cavity [15]. The second is vascular; high ACE2 expression in endothelial cells may play a role in trigeminovascular activation around the nasal and oral cavity, cephalic vessels and dura mater, leading to headache [16]. The third is the release of proinflammatory mediators and cytokines during COVID-19 infection triggers perivascular trigeminal nerve endings [17]. In addition to the trigeminal nerve, the vagus nerve is also increasingly described as a neuron invasion route. Although its role in headache is unclear, the vagus nerve has been proposed as a new therapeutic target for brain damage in COVID-19, although this...
requires further study [18]. Few studies have investigated COVID-19-related headache [19,20]. Uygun et al. described the headaches as bilateral, lasting longer than 72 h, resistant to analgesics, occurring more in males, and associated with mostly gastrointestinal (GI) symptoms and a loss of smell or taste [21]. Bolay et al. reported that the headaches are new-onset, moderate to severe, analgesic-resistant, bilateral with a pulsating or pressing quality, and exacerbated by bending over [17]. Membrilla et al. found moderate to severe bilateral frontal or holocranial headaches, with a pressing quality, aggravated by physical activity and coughing, with partial response to first-line analgesics [22]. Porta-Etessam et al. described the headaches as mostly holocranial, pressing, and exacerbated by activity [23]. Souza et al. reported they were dull aching, bifrontal, mild to moderate intensity, with complete resolution within a few days [24]. Therefore, we investigated the characteristics or COVID-19-related headache, and their relationship with clinical severity in the early phase in Kırşehir Province, also known as Central Anatolia.

2. Methods

2.1. Study population

The study was conducted at Ahi Evran University Medical School Training and Research Hospital in Kırşehir Province, Turkey, between January and May 2021. This prospective cross-sectional study enrolled 226 patients who developed headaches during acute COVID-19 infections, who agreed to participate. All of the patients were diagnosed with COVID-19 based on polymerase chain reaction positivity and were recruited from the pandemic outpatient clinic, which is accessible to the general population of Kırşehir Province. Patients under 18 years of age; with a history of cancer, chronic kidney or liver disease, or congestive heart failure; or who were pregnant or uncooperative were excluded.

2.2. Data collection

During the acute COVID-19 infection, demographic data, COVID-19-related headache characteristics, and infection symptoms were recorded within the first 48 h of hospital admission by a headache specialist. The same specialist also examined the differences between new-onset headache due to COVID-19 and previous headache if any. Headaches were classified according to the International Classification of Headache Disorders, 3rd edition (ICHD-3 criteria) [25]. Based on a visual analog scale, the headache was defined as mild (score 1–3), moderate (4–6), severe (score 7–8), or very severe (score 9–10) [26]. Regarding the clinical severity of COVID-19, the patients were divided into three groups: mild disease had no respiratory symptoms, no pulmonary radiological signs, and oxygen saturation levels (SpO2) ≥96 %; moderate disease had mild respiratory symptoms, radiological evidence of pneumonia, and 93 % < SpO2 < 96 %; and severe disease had SpO2 ≤ 93 % requiring supplemental oxygen [27].

The study protocol was approved by the Ahi Evran University Research Ethics Committee (approval number: 2021-01/04), and informed consent was obtained from all participants.

2.3. Statistical analysis

The statistical analyses were performed using SPSS Statistics for Windows, ver. 25.0. (IBM, Armonk, NY, USA). The assumption of normality for quantitative variables was tested using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Descriptive statistics are given as the mean ± standard or n (%). For the univariate analyses, the chi-square, Fisher’s exact, or Fisher–Freeman–Halton exact test, or one-way analysis of variance (ANOVA) was used depending on the type of variable and validity of assumptions. Duncan’s multiple comparison test was used as a post hoc test. In all statistical analyses, a p-value < 0.05 was considered statistically significant.

3. Results

Table 1 summarizes the baseline characteristics and comorbidities of the patients experiencing headache during COVID-19 infection. This study included 226 patients (136 females, 60.2 %; 123 healthcare workers, 54.4 %). Their mean age was 40.7 ± 13.9 years and their body mass index (BMI) was 26.3 ± 4.7 kg/m². The most common systemic comorbidities were hypertension (13.7 %), diabetes mellitus (10.2 %), and pulmonary (7.5 %), heart (7.5 %), and rheumatological (2.2 %) disease. The most common accompanying symptoms were arthralgia (61.9 %), asthenia (55.8 %), anosmia (53.5 %), ageusia (52.2 %), myalgia (46.5 %), cough (44.2 %), fever (39.4 %), sore throat (38.5 %), dyspnea (28.3 %), and nausea (27.4 %). Less frequent symptoms were diarrhea, photophobia, phonophobia, dizziness, abdominal pain, vomiting, and allodynia (Table 1).

Of the patients, 164 (72.5 %) reported a new-onset COVID-19-related headache as lasting 4 days, and mostly bilaterally or localized to the forehead (58.4 %), pulsating (42.5 %), of moderate to severe intensity (30.1 %), with a partial response (<50 %) to paracetamol, the only drug recommended for it in Turkey (23.5 %). Sixty-two patients (27.4 %) reported headaches before COVID-19; of these, 11 (17.7 %) had headaches similar to before, 16 (25.8 %) had somewhat different headaches, and 35 (56.4 %) had completely different headaches. Table 2 compares the headache characteristics before and after COVID-19 infection in patients with previous headaches. These patients reported that fiery type (p = 0.025), very severe intensity (p = 0.008), holocranial distribution (p = 0.004), and less response to paracetamol (p = 0.003) were significantly more frequent headache characteristics after COVID-19 compared to headaches before COVID-19.

Table 1

| Accompanying symptoms | n (%) |
|------------------------|-------|
| Arthralgia             | 140(61.9) |
| Asthenia               | 126(55.8) |
| Anosmia                | 121(53.5) |
| Ageusia                | 118(52.2) |
| Myalgia                | 105(46.5) |
| Cough                  | 100(44.2) |
| Fever                  | 89(39.4)  |
| Sore throat            | 87(38.5)  |
| Dyspnea                | 64(28.3)  |
| Nausea                 | 62(27.4)  |
| Diarrhea               | 46(20.4)  |
| Photophobia            | 39(17.3)  |
| Phonophobia            | 32(14.2)  |
| Dizziness              | 30(13.3)  |
| Abdominal pain         | 24(10.6)  |
| Vomiting               | 23(10.2)  |
| Allodynia              | 10(4.4)   |

Values are expressed as n(%) and mean ± SD.
Comparison of headache characteristics before and after COVID-19 infection in patients with previous headaches (n = 622).

| Headache types | Before COVID-19 n (%) | After COVID-19 n (%) | p  |
|----------------|-----------------------|----------------------|----|
| Pulsating      | 37(57.8)              | 26(40.6)             | 0.025 |
| Stabbing       | 1(1.6)                | 2(3.1)               |     |
| Pressing       | 21(32.8)              | 22(34.4)             |     |
| Fiery          | 3(4.7)                | 14(21.9)             |     |

Headache intensity

| Mild | Moderate | Severe | Very severe |
|------|---------|--------|-------------|
| 12(18.8) | 28(43.8) | 17(26.6) | 5(7.8) |

Bilateral and lasting more than 72 h, and bilateral, lasting longer than 72 h, analgesic resistant, occurring more often in males, with mostly GI symptoms and loss of smell or taste. They concluded that male sex, bilateral and lasting more than 72 h, and analgesic resistance are important for distinguishing COVID-19-positive patients with headache from negative ones [28]. Bolay et al. observed new-onset moderate to severe, bilateral headache with pulsating or pressing quality, exacerbated by bending over, localized in the temporal-parietal region in COVID-19 patients. They found the headaches were resistant to analgesics, and had a high relapse rate during the active COVID-19 phase [17]. Membria et al. found that COVID-19-related headache was mostly bilateral frontal or holocranial, moderate to severe, pressing quality, aggravated by physical activity and coughing, with partial response to first-step analgesics [22]. They observed that individuals with a history of migraine (25.3 %) were more likely to have earlier (at onset of respiratory symptoms), longer (>24 h), and more intense (VAS score >5) headaches [22]. In an observational study, Porta-Etessam et al. revealed that the COVID-19 headache is mostly holocranial, pressing, and exacerbated with activity [23]. Souza et al. reported that patients mostly described the headache as dull aching, bifrontal, mild to moderate intensity with complete resolution within 5 days [24]. In line with the literature, our subjects with new-onset headache described their pain as lasting for 4 days, and mostly less than 5 days [24]. In line with the literature, our subjects with new-onset headache described their pain as lasting for 4 days, and mostly less than 5 days [24]. In line with the literature, our subjects with new-onset headache described their pain as lasting for 4 days, and mostly less than 5 days [24]. In line with the literature, our subjects with new-onset headache described their pain as lasting for 4 days, and mostly less than 5 days [24]. In line with the literature, our subjects with new-onset headache described their pain as lasting for 4 days, and mostly less than 5 days [24].
COVID-19-related headache. Some have reported male dominance [22, 28] others have reported female dominance [23,24]. Most of our subjects were female, which may be attributed to the high enrollment of healthcare workers in this study, with most being female nurses. Significantly more females also had mild disease. There is some evidence that immune activity is more effective for viral infections in women [28]. It is thought that SARS-CoV-2 triggers some silenced genes related to innate immunity on the X chromosome, so the two X chromosomes make the immune pathways work more effectively and balanced against COVID-19-associated hyperactivation. Moreover, estrogens and progesterone have anti-inflammatory effects in some models, via inflammasome activation [29]. Furthermore, being a young university graduate may be another explanation, as low education level and advanced age were frequent in our patients with severe headache.

Comorbidities were also risk factors for increased mortality in COVID-19. A BMI greater than 28 kg/m² [30], diabetes mellitus [31], and hypertension [32] are reported independent risk factors associated with COVID-19 severity, and this was the case in our study.

In our subjects, arthralgia, myalgia, asthenia, agitation, and anosmia were more frequent accompanying symptoms in the COVID-19 patients with headache than diarrhea, photophobia, phonophobia, dizziness, and hypertension [32] are reported independent risk factors associated with COVID-19 severity, and this was the case in our study. Vaira et al. reported ageusia and anosmia, which work with headache than diarrhea, photophobia, phonophobia, dizziness, and advanced age were frequent in our patients with severe headache.

Similarly, olfactory disorder was more common in our patients in the mild group. In one study, GI symptoms including diarrhea, abdominal transport [9] are increased in response to activation of the gut virus spread in the host, suggesting it is a good prognostic factor [35].

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The study had some limitations. First, it is necessary to validate these findings with a larger cohort to reach more definitive conclusions. Second, we did not analyze cytokines, preventing us from clarifying the underlying mechanisms. Third, there was no control group, because we focused mainly on the headache characteristics in a group of COVID-19-positive patients.

In conclusion, neurological symptoms, particularly headache, are common in patients with COVID-19 infection. We found that bilateral, long-lasting, moderate to severe headaches resistant to analgesics were more frequent in COVID-19 patients in Kirşehir Province, Turkey. Large-scale trials are needed to reveal whether the headache characteristics are useful for distinguishing COVID-19-related headaches from other types, particularly in otherwise asymptomatic subjects.

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