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Clinical Neurology and Neurosurgery 219 (2022) 107339

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Full length article

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

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ARTICLE INFO

Keywords:
COVID-19
Headache
Neurological manifestations
SARS-CoV-2 virus
Neuroinvasion

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 Kırşehir 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

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https://doi.org/10.1016/j.clineuro.2022.107339
Received 1 March 2022; Received in revised form 9 June 2022; Accepted 12 June 2022
Available online 14 June 2022
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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 (SpO_2) ≥96 %; *moderate disease* had mild respiratory symptoms, radiological evidence of pneumonia, and 93 % <SpO_2 < 96 %; and *severe disease* had $SpO_2 \leq 93$ % 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 analyzes, 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/m^2. 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
The baseline characteristics of the patients experiencing headache during COVID-19 infection ($n = 226$).

	n (%)
Age (years)	40.76 ± 13.90
Gender (female/male)	136(60.2)/90(39.8)
Body mass index	26.33 ± 4.70
Healthcare worker	123(54.4)
Marital status	
Married	165(73.0)
Single	60(26.5)
Education level	
Illiterate	8(3.5)
Primary and secondary school	41(18.1)
High school	41(18.19)
University	136(60.2)
Systemic comorbidities	
Hypertension	31(13.7)
Diabetes mellitus	23(10.2)
Pulmoner disease	17(7.5)
Heart disease	17(7.5)
Rheumatological disease	5(2.2)
Accompanying symptoms	
Artralgia	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)
Vomitting	23(10.2)
Allodynia	10(4.4)

Values are expressed as n(%) and mean ± SD.

Table 2
Comparison of headache characteristics before and after COVID-19 infection in patients with previous headaches ($n = 62$).

	Before COVID-19 *n (%)*	After COVID-19 *n (%)*	*p*
Headache types			
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	12(18.8)	7(10.9)	0.008
Moderate	28(43.8)	18(28.1)	
Severe	17(26.6)	20 (31.3)	
Very severe	5(7.8)	19(29.7)	
Headache localization			
Bilateral	36(56.3)	29(45.3)	0.004
Unilateral	19(29.7)	12(18.8)	
Whole	7(10.9)	23(35.9)	
Forehead	32(50.0)	34(53.1)	0.865
Vertex	13(20.4)	32(50.0)	0.001
Temple	22(34.4)	36(56.3)	0.019
Back neck	20(31.3)	34(53.1)	0.018
Orbital	15(23.4)	26(40.6)	0.049
Face	9(14.1)	22(34.4)	0.011
Response to paracetamol			
No paracetamol use	3(4.7)	4(6.3)	0.003
No response to paracetamol	7(10.9)	17(26.6)	
Partial response to paracetamol <50 %	13(20.3)	19(29.7)	
Improved with paracetamol >50 %	12(18.8)	16(25.0)	
Completely recovered with paracetamol	27(42.2)	8(12.5)	

Values are expressed as n(%).

Table 3
Correlation analysis between baseline data and COVID-19 clinical severity.

	Mild (n=138)	Moderate (n=46)	Severe (n=42)	*p*
Age (years)	36.56 ± 11.60a	37.73 ± 9.48a	57.85 ± 11.99b	0.000
Female gender	77(56.6)	36(26.5)	23(16.9)	0.019
BMI (kg/m^2)	25.61 ± 4.50a	26.19 ± 4.92a	28.85 ± 4.35b	0.000
Marital status				
Single	93(56.4)	36(21.8)	36(21.8)	0.159
Married	44(73.3)	10(16.7)	6(10.0)	
Education level				
Illiterate	1(12.5)	0(0.0)	7(87.5)	0.000
Primary and secondary school	15(36.6)	8(19.5)	18(43.9)	
High school	28(68.3)	3(7.3)	10(24.4)	
University	94(69.1)	35(25.7)	7(5.1)	
Healthcare worker	83(67.5)	32(26.0)	8(6.5)	0.000
Systemic comorbidities				
Hypertension	9(29.0)	6(19.4)	16(51.6)	0.000
Diabetes mellitus	9(39.1)	4(17.4)	10(43.5)	0.005
Pulmoner disease	5(29.4)	3(17.6)	9(52.9)	0.001
Heart disease	10(58.8)	1(5.9)	6(35.3)	0.097
Rheumatological disease	3(60.0)	2(40.0)	0(0.0)	0.383
Accompanying symptoms				
Nausea	35(56.5)	12(19.4)	15(24.2)	0.409
Vomitting	11(47.8)	5(21.7)	7(30.4)	0.260
Photophobia	25(64.1)	10(25.6)	4(10.3)	0.290
Phonophobia	18(56.3)	13(40.6)	1(3.1)	0.002
Allodynia	6(60.0)	0(0.0)	4(40.0)	0.095
Fever	47(52.8)	23(25.8)	19(21.3)	0.110
Cough	50(50.0)	20(20.0)	30(30.0)	0.000
Sore throat	58(66.7)	17(19.5)	12(13.8)	0.284
Artralgia	83(59.3)	33(23.6)	24(17.1)	0.290
Myalgia	59(56.2)	25(23.8)	21(20.0)	0.346
Asthenia	79(62.7)	28(22.2)	19(15.1)	0.287
Diarrhea	20(43.5)	10(21.7)	16(34.8)	0.004
Abdominal pain	17(70.8)	4(16.7)	3(12.5)	0.567
Dyspnea	12(18.8)	10(15.6)	42(65.6)	0.000
Ageusia	75(63.6)	24(20.3)	19(16.1)	0.585
Anosmia	84(69.4)	24(19.8)	13(10.7)	0.003
Dizziness	17(56.7)	7(23.3)	6(20.0)	0.862

Values are expressed as n(%) and mean ± SD.

Table 3 shows the results of correlation analysis between the baseline data and COVID-19 clinical severity. Regarding the clinical severity of COVID-19, there were 138 (61.1 %), 46 (20.4 %), and 42 (18.5 %) patients in the mild, moderate, and severe groups, respectively. Older age, high BMI, and low education level were significantly more common in the severe group (all $p < 0.001$). Female sex ($p = 0.019$) and being a healthcare worker ($p < 0.001$) were significantly more common in the mild cases. Comorbid hypertension ($p < 0.001$), diabetes mellitus ($p = 0.005$), and pulmonary disease ($p = 0.001$) were significantly more frequent in the severe group. Accompanying phonophobia ($p = 0.002$), cough ($p < 0.001$), diarrhea ($p = 0.004$), and anosmia ($p = 0.003$) were reported significantly more often in the mild group, whereas dyspnea was more common in the severe group ($p < 0.001$).

4. Discussion

Our main findings are that new-onset COVID-19-related headache is long-lasting and mostly bilaterally or localized to the forehead, pulsating type, and moderate to severe intensity, and it partially responds to analgesics. Another is that being fiery type, very severe intensity, and a holocranial distribution and less responsive to analgesics were significantly more frequent headache characteristics after COVID-19 than before COVID-19 in patients with a previous headache.

COVID-19-related headache is classified in the ICHD-3 section on headache associated with systemic viral infection (without signs of meningo-encephalitis) secondary to the primary disease (ICHH-39.2.2). This classification characterizes the headache as diffuse, moderate, or severe, and usually accompanied by fever, although the underlying mechanisms are not yet clear [25]. There are few published studies of COVID-19-related headache. Uygun et al. described the headache as 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 temporoparietal 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]. Membrilla 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 bilaterally or localized in the forehead, pulsating type, moderate to severe intensity, with a partial response to analgesics. In about half of our patients (56.4 %) with headaches before COVID-19, their new pain was different with fiery type, high intensity, holocranial location, and more resistance to analgesics. Overall, the headache characteristics are similar in various studies, which may reflect the shared pathophysiological mechanisms causing headache associated with COVID-19.

However, there have also been some differences among studies of

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, ageusia, and anosmia were more frequent accompanying symptoms in the COVID-19 patients with headache than diarrhea, photophobia, phonophobia, dizziness, and allodynia. The literature reports that the prevalence of anosmia is heterogeneous at 5–85 % [33]. The suggested mechanism involves virus spread from the nasal cavity to the olfactory bulb, and then to the brainstem via the piriform cortex by both passive diffusion and axonal transport [9]. Vaira et al. reported ageusia and anosmia, which work together, in 19.4–88 % of COVID-19 patients [34]. Lechien et al. stated that the spread of SARS-CoV-2 to the olfactory neuroepithelium and olfactory bulb induces a local immunological reaction, which limits virus spread in the host, suggesting it is a good prognostic factor [35]. Likewise, olfactory disorder was more common in our patients in the mild group. In one study, GI symptoms including diarrhea, abdominal pain, and nausea were reported in more than half of some COVID-19 cases with headache [28]. Similarly, Jin et al. found a high concomitance of headache with GI symptoms [36]. Data suggest that circulating levels of inflammatory mediators such as interleukin-1β (IL-1β), IL-6, and IL-8 are increased in response to activation of the gut–brain axis [37]. Neuropeptides containing tumor necrosis factor-α and calcium gene-related peptide are thought to be other contributors to this activation. These cytokines may trigger both headache via trigeminovascular activation and diarrhea by increasing the GI motility in a vicious circle [17,37]. In line with this, GI symptoms are expected to be high in the severe group with further inflammation and vascular edema [36]. However, we frequently observed diarrhea in the mild group. This may be explained by the local microbiota being partially unresponsive to COVID-19, or simply as a result of the large number of patients in the mild group.

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 Kırşehir 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.

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see:

http://www.textcheck.com/certificate/JBmMsC.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Concept/Design: BES; **Data Collection and/or Processing:** BES, AC; **Data analysis and interpretation:** BES, AC; **Literature Search:** BES, AC, YK, LH; **Drafting manuscript:** BES, AC, YK, LH; **Critical revision of manuscript:** BES, AC; **Supervision:** AC.

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