Neurology Asia 2021; 26(1) : 101 – 106

COVID-19 related headache and its clinical characteristics

[1]Banu Özen Barut *MD*, [1]Samiye Ulutaş *MD*, [1]Gülhan Şahbaz *MD*, [1]Afra Çelik *MD*, [1]Tuğçe Şule Kara *MD*, [2]Pınar Öngörü *MD*

[1]Department Of Neurology and [2]Department of Infectious Diseases,University of Health Sciences, Kartal Dr. Lütfü Kırdar City Hospital, İstanbul, Turkey

Abstract

Objectives: Headache is one of the most common neurological symptoms in COVID-19 patients. This study examined the prevalence of headache and its clinical properties in patients with COVID-19. *Methods:*This was a prospective, cross-sectional study of laboratory-confirmed COVID-19 pneumonia patients from a neurology inpatient ward. Data for COVID-19-positive patients aged between 17 and 88 years were analyzed, based on the results of real-time polymerase chain reaction (rPCR) for SARS COV-2. Headache prevalence and characteristics and routine laboratory examinations were investigated. *Results:* The study analyzed 209 consecutive COVID-19 patients. Of these, 142 (67.9%) patients suffered headaches during COVID-19 infection and 107/209 (51.2%)patients reported a new type of headache. Of the209 patients, 101 (48.3%) also described decreases in smell and taste during the headache. The most common headache location was fronto-orbital, in 52/142 (40.6%) patients. Most patients had a bilateral headache (90.8%).
Conclusion: As our knowledge of COVID-19 accumulates, we find that COVID-19 headache is not a random symptom. A new or different kind of throbbing headache that is bilateral and fronto-orbital might be related to COVID-19 disease.

Keywords: Headache, pain, COVID19, infection, corona virus

INTRODUCTION

Several neurological symptoms have been described in COVID-19 infection, of which headache is the most common.[1] However, headache and its clinical properties were not the primary end point in most of these studies. Recently, Megemont *et al*. investigated headache prevalence by interviewing patients retrospectively and found that 59% of the patients experienced headache during COVID-19 infection.[2]However, they did not study the clinical characteristics of the COVID-19 headache.

Therefore, we analyzed the prevalence and characteristics of headache in COVID-19-positiveneurology inpatients during the COVID-19 pandemic. Most of the studies focusing on the characteristics and properties of the headache have been retrospective. We study the characteristics of COVID-19-related headache prospectively.

METHODS

This descriptive, cross-sectional study was conducted in Turkey between April and June 2020. All patients were from Dr. Lütfi Kirdar City Hospital. The study was approved by the ethics committee of Dr.Lütfi Kirdar City Hospital. Patients were invited to participate, and informed consent was obtained from all participants. Our neurology clinic followed 308 patients who had pneumonia of unknown etiology between April and June 2020. These patients were suspected of having COVID-19 pneumonia, based on their clinical examination and chest computed tomography (CCT). All patients were assessed with real-time polymerase chain reaction (rPCR), CCT, and routine laboratory tests including a hemogram, blood biochemistry, and coagulation parameters. Inclusion criteria were patients over 17 years old with suspected COVID-19 pneumonia.

Address correspondence to: Banu Özen Barut,Kartal Dr. Lütfü Kırdar City Hospital, Neurology Department İstanbul, Turkey. Tel: 05337351263, E mail: banuozenbarut@gmail.com

Date of Submission: 9 February 2021; Date of Acceptance: 12 February 2021

In March 2020, the World Health Organization announced a pandemic and the COVID-19 outbreak in Turkey started escalating. Our neurology clinic was assigned to be a COVID-19 inpatient care department in March 2020. While we were treating our patients, we found that most of them suffered from headache. Patients who were initially diagnosed with COVID-19 were followed by the neurology staff working in this clinic and the subjects recruited to this study were on the neurology ward between April and June 2020. The sample size was based on the available data. All patients were interviewed in person and asked about the presence of headache during the course of COVID-19 infection. Patients who had a headache during the interview or anytime during the disease course were deemed headache positive. The headache features of the cases were investigated, including localization, laterality, and severity. A visual analog scale (VAS) was used to assess the headache severity. Participants were asked to specify their pain intensity on a scale from zero to 10. Patients were asked about accompanying features, like nausea and vomiting, light and voice sensitivity, and loss of taste and smell. We also asked about the patients' headache history before COVID-19 infection and tried to differentiate COVID-19-related headache by asking three questions:

- Have you had frequent headaches before?
- Does the headache you have now resemble the type of headache you experienced before?
- Is the headache you are suffering now a different type of headache?

The patients' answers were recorded by the neurology residents. Our study is important in that it is the first to focus on headache prevalence in COVID-19 patients and its clinical properties.

SPSS 25.0 was used for all statistical analyses. Descriptive statistics of continuous variables were given as the mean, standard deviation, and range, while frequency and percentage were used for categorical variables. The Shapiro Wilk test was used as a test of normality. To compare two independent groups, the independent samples *t*-test was used for normally distributed variables and the Mann–Whitney *U*-test for non-normally distributed variables. To compare two dependent groups, the similarly paired samples *t*-test was used to compare normally distributed variables and the Wilcoxon test for non-normally distributed variables. The chi-square test was used to compare categorical variables. For all statistical comparisons, $p<0.05$ was assumed to indicate statistical significance.

RESULTS

Between April and June 2020, 308 patients were admitted with pneumonia of unknown cause. Of these, 99 patients with negative SARS COV2 rPCR results were excluded. Table 1 summarizes the demographic data of the 209 patients with positive rPCR results. The average age was 53.3±14.77 years, with 110 (50.7%) males and 99 (49.3%) females. The hospitalization duration was 7.57±5.16 days (SD); 12 patients were transferred to the intensive care unit (ICU) and one patient died.

During COVID-19 infection,142 (67.9%) patients suffered headaches. Seventy (33.5%) patients had experienced headaches before COVID-19and 107 patients (51.2%) reported a new type of headache. Of the 209 patients, 101 (48.3%) also described decreased smell and taste. Table 2 summarizes the clinical properties of the patients with headache. The average VAS pain score of patients with headaches was 5.91±2.32. The most common headache localization was fronto-orbital, described by 52 (40.6%)of the 142 headache sufferers. This was followed by diffuse (n=31, 21.8%) and vertex (n=31,21.8%) localizations. The headache was bilateral in 132(90.8%) patients. We classified the headache type as throbbing, compressive, dull, stabbing, combined, and other. The most common type of headache was throbbing (n=65, 45.8%), followed,in order,by compressive, dull, combined, and stabbing. Nausea and vomiting occurred in 83 (58.5%) patients and 30 (21.1%) described light and voice sensitivity during COVID-19-related headaches.

Table 3 compares the clinical and laboratory properties of the patients with and without headaches during COVID-19 infection. Patients with headaches were younger than those without headaches ($p=0.014$). There was no significant difference between the two groups according to gender ($p=0.357$). There were 59 (84.3%) patients who had previously had headache attacks in the headache-positive group, while 59.7% of the patients who had not had previous headaches reported a headache during the COVID-19 infection. The difference was significant ($\chi^2=12.907$, $p<0.05$). The hemogram, white blood cell number, and D dimer did not differ significantly between the two groups ($p=0.370$, $p=0.052$, and $p=0.069$, respectively), while C-reactive protein was significantly higher in the headache-negative group ($p=0.012$). Hospitalization length, which could be related

Table 1: Demographic findings and headache frequency of COVID-19 patients followed up in neurology ward

COVID-19 (+) PATIENTS (N)	N=209
Female/Male (%)	99/110 (47.3%/ 50.7%)
Age, year (mean, SD)	53.3 (14.77)
Age, year (median) (min-max)	54 (17-88)
Length of hospital stay, day mean (SD)	7.57 (5.16)
Length of hospital stay, day median (min-max)	6 (2-34)
Number of patients transferred to intensive care unit (n, %)	12 (5.7 %)
Hemoglobin (g/dl), mean (SD)	12.97 (1.74)
Hemoglobin (g/dl), median (min-max)	13.1 (12-23.6)
White blood cell number, mean (SD)	6,247.12 (2,801.18)
White blood cell number, median (min–max)	5,750 (1,200-23,600)
C reactive protein (mg/L), mean (SD)	54, 96 (58.11)
C reactive protein (mg/L), median (min–max)	33.80 (3-294)
D dimer (ng/dl), mean (SD)	1,088.08 (1,633.81)
D dimer (ng/dl), median (min–max)	645 (140-18,410)
Patients suffer headache during COVID19 infection (n, %)	142 (67.9 %)
Patients suffer headache before COVID-19 infection (n, %)	70 (33.5 %)
Patients describe headache similar to headache before COVID-19 infection (n, %)	44 (%21.1)
Patients describe headache new or different from previous headache (n, %)	107 (%51.2)
Patients who describe taste and smell loss during COVID-19 infection (n, %)	101 (%48.3)

Table 2: Clinical and laboratory properties of headache positive COVID-19 patients

COVID-19 patients suffering from headache (n)	142
VAS mean (SD)	5.91 (2.32)
VAS Median (min-max)	6 (2-10)
Localization n (%)	
• Fronto-orbital	52 (40.6)
• Parieto-occipital	28 (19.7)
• Vertex	31 (21.8)
• Global	31 (21.8)
Lateralization, n (%)	
• Unilateral	13 (9.2)
• Bilateral	129 (90.8)
Headache type, n (%)	
• Throbbing	65 (45.8)
• Compressive	47 (33.1)
• Dull	16 (11.3)
• Combined	6 (4.2)
• Stabbing	5 (3.5)
• Could not describe	3 (2.1)
Nausea and vomiting, n(%)	83 (58.5)
Voice and light sensitivity, n (%)	30 (21.1)
Lateralization, n (%)	13 (9.1)
Loss of taste and smell, n (%)	81 (57)

Table 3: Comparison of patients with headache and without headache

Number of patients (n)	Headache positive (142)	Headache negative (67)	P
Age, years (mean, ±SD)	51.61 (±14.97)	56.97 (±13.75)	**0.014**
Gender Female % Male %	69 (48.6 %) 73 (51.4%)	30 (44.8 %) 37 (55.2%)	X^2= 0.266 p=0.357
Hospital stay length, day (mean, ±SD)	7.23 (±4.62)	8.3 (±6.1)	0.207
Number of Patients transferred to intensive care unit (%)	8 (5.6)	4 (6)	X^2=0.481 P=0.786
Hemoglobin (g/dl), (mean, ±SD)	13.05 (±1.80)	12.81 (±1.61)	0.370
White blood cell number (mean, ±SD)	5,945 (±2,309)	6,882 (±3,562)	0.052
C reactive protein (mg/L), (mean, ±SD)	49.67 (±56.15)	66.16 (±60.98)	**0.012**
D Dimer (ng/dl), mean, ±SD)	1,073.28 (±1,871.03)	1,118.12 (±1,003.91)	0.069
Patients suffer headache before COVID-19 infection, n (%)	59 (84.3)	11 (15.7)	**X^2=12.907 p<0.05**
Patients who describe loss of taste and smell during COVID-19 infection, n (%)	81 (57)	20 (29.9)	**X^2=13.478 p<0.05**

to disease severity, was not significantly different between the two groups (p=0.207). The proportions of patients transferred to the ICU were similar in the headache-positive and -negative groups (Table 3). Of the patients who stated that they had headache attacks during COVID-19 infection, 57% reported loss of taste and smell versus 30% of the patients who did not report any headache attacks during COVID-19 infection. The difference between these groups was significant (χ^2=13.478, p<0.05).

DISCUSSION

COVID-19 pneumonia is caused by the SARS COV2 virus, which is one of the seven members of the coronavirus family. Four of these species cause simple common colds, whereas three of them(SARS COV, MERS COV, and SARS COV2) cause a more severe clinical presentation related to SARS COV2.[3] The most common clinical findings are fever, cough, myalgia/fatigue, dyspnea, and headache. Neurological manifestations such as dizziness, headache, cerebrovascular disorders, impaired consciousness, transverse myelitis, acute hemorrhagic necrotizing encephalopathy, encephalitis, and epilepsy indicate central nervous system involvement, whereas hypogeusia, hyposmia, Guillain–Barre syndrome, neuralgia, and skeletal muscle injury indicate peripheral nervous system involvement.[4] Our study investigated the prevalence of headache in COVID-19 patients and compared the clinical characteristics and outcomes of COVID-19 patients with and without headache. The prevalence of headache was 67.9% in our sample, which was higher than the reported rates between6.5 and 59%.[2,5-10] The higher headache prevalence is thought to be related to our study design. All the studies that documented headache prevalence were retrospective, so mild headache could have been under-diagnosed during the pandemic. We also compared our results with other upper respiratory system viral infections. In a prospective study, Eccles *et al*. found that 60% of patients experienced headache during upper respiratory tract infection (URTI)[11], similar to our study. Tyrell *et al*. reported that patients with five types of URTI, including coronavirus, frequently described headaches and the percentage of patients with headaches was between 27% and 50% in each group. The percentage of coronavirus patients with headaches was 32%.[12] The most common headache type in our patients was a bilateral throbbing headache, and the pain was commonly described in the fronto-orbital region. Headache properties have not been studied in COVID-19 patients before, but a review of headaches in COVID-19 patients described a moderate to severe, throbbing type in the temporoparietal area based on clinical observations. That review explained the pathogenesis of headache in COVID-19 patients using three possible mechanisms: 1)direct invasion of the trigeminal nerve ending in the nasal cavity by SARS COV2

virus; 2)involvement of endothelial cells with high expression of ACE 2, which is thought to play a role in the trigemino-vascular activation type headache; and3)proinflammatory mediators and cytokines related with the virus.[13] In our study, the inflammation marker CRP was significantly lower in the headache-positive group, which counters the inflammation hypothesis. Low CRP levels can be related to disease distribution. Disease located in the upper respiratory tract might have a lower CRP and more headaches compared with lower respiratory involvement. Further studies can examine this hypothesis. According to Mao *et al*., headache is more common in severe COVID-19 than in milder cases.[14] We did not evaluate the severity of COVID-19. Neither hospitalization duration nor the ICU transfer rate differed between our headache-positive and -negative patients. We did not analyze the CCT results that might be related to disease severity. Therefore, a more detailed prognostic factor assessment maybe valuable in future studies. Zhang *et al*. reported that headache is more common in patients with abnormal CCT findings.[15] Further studies that include CCT and inflammatory mediators could be useful for understanding disease pathogenesis and severity.

One of the goals of this study was to differentiate the patients who had already had primary types of headache from those with a new or different type of headache related to COVID-19. The latter was described by 51.2% of the COVID-19 patients, whereas 21.1% described a headache similar to those previously experienced. Therefore, we conclude that COVID-19 patients experience a different type of headache in the course of the infection. However, more patients with a headache history tend to experience headache during COVID-19 infection. The headache-positive patients were significantly younger than those without headache, which could be explained by the fact that headache prevalence decreases with aging.[16]

The patients experiencing headache also had significantly more complaints about loss of taste and smell. The mechanism of smell and taste loss in COVID-19 patients has not been clearly explained. Two possible explanations have been used to explain the pathogenesis: 1)nasal inflammation and mucosal edema related to upper respiratory infection or 2)possible peripheral nerve [olfactory nerve]involvement in COVID-19 patients.[17] The olfactory nerve is unique in that it is the only sensory cranial nerve that projects directly to the cerebral cortex, indirectly via the thalamus, so its close relation to the cerebrum might be responsible for the association of olfactory loss and headache, which is a central nervous system symptom.[18]

Our study has some limitations. First, a more detailed, validated headache questionnaire should have been used to investigate headache but, due to limitations related to the diffusivity of the disease and emergency contingencies, we used a short-term assessment. Second, clinical factors like fever, saturation, and CCT could be analyzed to find correlations with headache and to understand the relationship.

In conclusion, physicians should be alert to the presence of a new or different kind of headache in COVID-19 patients. The headache linked to COVID-19 is not a random symptom but has specific properties.

ACKNOWLEDGMENT

Authors thank to Professor Dr. Çagatay Barut for the support given during the statistical analyses of the study.

DISCLOSURE

Financial support: None

Conflict of interest: None

REFERENCES

1. Berger JR. COVID-19 and the nervous system. *J Neurovirol* 2020;26(2):143-8.
2. Poncet-Megemont L, Paris P, Tronchere A, *et al*. High prevalence of headaches during Covid-19 infection: A retrospective cohort study. *Headache* 2020 Aug 5:10.1111/head.13923
3. Belvis R. Headaches during COVID-19: My clinical case and review of the literature. *Headache* 2020;60(7):1422-6.
4. Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: A literature review. *J Clin Neurosci* 2020;77:8-12..
5. Chen N, Zhou M, Dong X, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel corona virus pneumonia in Wuhan, China: A descriptive study. *Lancet* 2020;395:507-13.
6. Liu M, He P, Liu HG, *et al*. Clinical characteristics of 30 medical workers infected with new corona virus pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi*2020;43:209-14.
7. Tian S, Hu N, Lou J,*et al*. Characteristics of COVID-infection in Beijing. *J Infect* 2020;80:401-6.
8. Jin X, Lian JS, Hu JH, *et al*. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut* 2020;320926.
9. Xu XW, Wu XX, Jiang XG, *et al*. Clinical findings

in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: Retrospective case series. *BMJ* 2020;368:792.
10. Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497-506
11. Eccles R, Loose I, Jawad M, *et al*. Effects of acetylsalicylic acid on sore throat pain and other pain symptoms associated with acute upper respiratory tract infection. *Pain Med* 2003;4:118-24.
12. Tyrrell DA, Cohen S. Schlarb JE. Signs and symptoms in common colds. *Epidemiol Infect* 1993;111: 143-56.
13. Bolay H, Gül A, Baykan B. COVID 19 is a real headache. *Headache* 2020;60(7):1415-21..
14. Mao L, Jin H, Wang M, *et al*. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020; 77(6):683-90.
15. Zhang X, Cai H, Hu J, *et al*. Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings. *Int J Infect Dis* 2020;94:81-7.
16. Tanganelli P. Secondary headaches in the elderly. *Neurol Sci* 2010;31(Suppl. 1):S73-S76.
17. Izquierdo-Dominguez A, Rojas-Lechuga MJ, Mullol J, Alobid I. Olfactory dysfunction in the COVID-19 outbreak. *J Investig Allergol Clin Immunol* 2020;30(5):317-26.
18. Standring S. Gray's Anatomy: The anatomical Basis of clinical Medicine. 41st Ed. Edinburgh Elsevier. 2016:231.