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# Headaches associated with acute SARS-CoV-2 infection: A prospective cross-sectional study

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**Abstract**

**Objectives:** The prevalence and characteristics of COVID-19-related headaches are not known in Indian patients. We aim to determine the prevalence and characteristics of headache in COVID-19-infected individuals and make a comparison with those without headaches.

**Methods:** This prospective cross-sectional observational study was conducted from 1 October to 31 October 2020. Data were collected using a detailed questionnaire. We compared the data of those with and without headaches to identify the differences between the groups.

**Results:** During the study period of 1 month, among 225 COVID-19-infected patients, 33.8% patients had headaches. The mean age of patients with headache was 48.89 ± 15.19 years. In all, 53.9% were females. In 65.8%, headache occurred at the onset of viral illness; 44.7% described the headache as dull aching; 39.5% had bifrontal headache; and 32.9% had holocranial headache. In total, 78.9% had complete resolution of headache within 5 days. A comparison between those with and without headaches showed that those with headaches were more younger (48.89 ± 15.19 vs 54.61 ± 14.57 years, $p = 0.007$) and of female gender (41/76(53.9%) vs 41/149 (27.5%), $p = 0.001$). Primary headache disorders were more common in the headache group. Levels of inflammatory markers such as leukocyte count (7234.17 ± 3054.96 vs 8773.35 ± 5103.65, $p = 0.017$), erythrocyte sedimentation rate (39.28 ± 23.29 vs 50.41 ± 27.61, $p = 0.02$) and ferritin (381.06 ± 485.2 vs 657.10 ± 863.80, $p = 0.014$) were lower in those with headaches.

**Conclusions:** Headaches are a common and early symptom of acute SARS-CoV-2 infection more frequently seen in young females and in those with a history of primary headache disorders. The lower level of inflammatory markers in those with headaches suggests that these headaches are probably due to the local spread of virus through the trigeminal nerve endings, resulting in activation of the trigeminovascular system.

**Keywords**

COVID-19, SARS-CoV-2, headache, migraine, tension-type headache, calcitonin gene–related peptide

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## Introduction

Coronavirus disease-19 (COVID-19) infection due to severe acute respiratory syndrome virus corona virus 2 (SARS-CoV-2) has created a massive global health crisis in 2020. India has presently the second largest number of COVID-19 cases in the world. SARS-CoV-2 virus though initially considered a primary respiratory pathogen is now known to be neurotrophic and neuroinvasive.[1] The neurological symptoms of COVID-19 infection are diverse, ranging from headache, anosmia, aguesia and seizure, to severe complications such as stroke, Guillain-Barre syndrome and encephalopathy.[1–3] Headache is one of the most common symptoms associated with COVID-19 infection and can be an inaugural and isolated symptom of COVID-19 infection.[4] The prevalence and

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characteristics of COVID-19-related headache (CRH) in Indian patients and its prognostic value are not known. As the number of COVID-19 patients increased at our centre, neurologists were pooled in to treat COVID-19-infected patients. Although this was a great challenge, it gave us an opportunity to evaluate neurological manifestations in COVID-19 patients. We hypothesized that headache is a common and early symptom of COVID-19 infection, with uncertain prognostic value. In this study, we aimed to analyse the characteristics of headache and its relation to other symptoms and laboratory markers. We also compared the characteristics of those with and without headaches to identify any differences between the groups.

## Methods

### Study design

This was a prospective cross-sectional observational study carried out at a single tertiary care centre in South India. The study period was from 1 October to 31 October 2020. The study was approved by the Institutional Review Board of St. John's Medical College Hospital, Bengaluru, India (IEC Study Ref No.358/2020).

### Study population

COVID-19 patients admitted to the infectious disease isolation wards and directly under the treatment of the neurology team were included in this study. All the patients were above the age of 18 years, and COVID-19 infection was confirmed with reverse transcription polymerase chain reaction (RT-PCR) testing using samples from nasopharyngeal swabs. Patients with altered sensorium, encephalopathy, meningitis, focal neurological deficits and severe respiratory distress were excluded from the study. A written informed consent was taken from all the study participants. In all patients, routine laboratory tests including complete blood count and renal function tests and inflammatory markers including D-dimer, ferritin, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were performed. Neuroimaging was not done in any of the patients.

### Data collection

A detailed questionnaire designed by senior neurologists, who were headache specialists, was used for this study. The questionnaire comprised the following subsections: 1. Demographic data (age, sex, medical comorbidities); 2. Headache characteristics (onset, location, nature, severity, duration and frequency); 3. Associated symptoms (photophobia, phonophobia, nausea/vomiting); and 5. Past history of primary headache disorders as classified by International Classification of Headache Disorders 3 (ICHD3).[5,6] Symptoms of COVID-19 were fever, anosmia, myalgia, cough, dyspnoea, sore throat, diarrhoea and confusion. The headache severity was rated using a numerical rating score (NRS) ranging from 0 to 10 (0 – no pain; 1 to 3 – mild pain; 4 to 6 – moderate pain; 7 to 9 – severe pain; 10 – very severe pain).[6] The questionnaire was administered as a face-to-face interview in English, Kannada or Telugu by neurologists proficient in these languages, which are the local languages of the population. The data collected were entered in a predesigned proforma sheet. The data were transferred to Microsoft excel and SPSS 25 after anonymising patient details to maintain confidentiality.

### Statistical analysis

Sample size was calculated based on previous studies that had shown a headache prevalence of 68.3%.[7] A sample size of 220 was determined to be adequate for a precision of 9% and confidence interval (CI) of 95%. Convenience sampling method was used. Descriptive statistics including mean, standard deviation and percentages were used to summarize the data. For comparison between the two groups with and without headaches, a Pearson's chi-square test was performed for categorical variables, and an independent Student's 't' test was performed for continuous variables. All tests were two-tailed, and a value of $p \leqslant 0.05$ was considered statistically significant. All statistical analyses were conducted with the SPSS statistical package for Windows, Version 25 (IBM).

## Results

During the study period of 1 month, there were 225 patients with acute SARS-CoV-2 infection. Of these 225, 76 patients (33.8 %) had headaches. The mean age of patients with headache was $48.89 \pm 15.19$ years, with 53.9% (41/76) being females. The mean age of patients without headaches was $54.61 \pm 14.57$ years, with 72.4% (108/149) being males. The proportion of patients having headache was the highest in the age group of 31–40 years (51.5%) and in the age group of 21–30 years (47.6%), while it was 24.3% in the age group of 41–50 years, 30.3% in the age group of 51–60 years and 29.8% in those above 60 years.

### Time of headache onset in relation to systemic symptoms

In 65.8% (50/76), headache occurred at the onset of viral illness, concurrent with other symptoms of fever, sore throat or cough. In 21.1% (16/76), headache developed 2–5 days after the systemic symptoms. In 11.8% (9/76), headache developed 6–10 days after the onset of systemic symptoms. In 1 patient (1.3%), headache developed 10 days after the initial symptoms.

### Nature of headache

In all, 44.7% (34/76) described the headache as dull aching, while 23.7% (18/76) had a throbbing pain. Furthermore,

23.7% (18/76) described the nature of headache as pulling, while 7.9% (6/76) had a pressing quality of headache.

### Site of headache

The site of headache was bifrontal in 39.5% (30/76) of patients, while 32.9% (25/76) had holocranial headache, 10.5% (8/76) bitemporal headache, 5.3% (4/76) bilateral occipital headache, 9.2% (7/76) hemicranial headache and 2.6% (2/76) headache over the vertex.

### Duration of headache

The headache was short-lived and resolved completely in most patients. In all, 78.9% (60/76) had headache lasting less than 5 days, 42.1% (32/76) had headache lasting less than 1 day, while 36.8% (28/76) had headache for 2–5 days. In addition, 6.6% (5/76) had headache lasting 6–10 days, and 14.5% (11/76) patients had headache for more than 10 days.

### Severity of headache

The headache was of mild to moderate intensity in the majority of patients. Totally, 25% (19/76) of patients had mild headache (NRS 1–3), while 56.6% (43/76) of patients had moderate headache (NRS 4–6). Only 18.4 % (14/76) of patients had severe headache (NRS 7–9). None of the patients described the headache as very severe (NRS 10)

### Associated symptoms

In total, 55.3% (42/76) had photophobia, while 52.6% (40/76) had associated phonophobia. Furthermore, 10.5% (8/76) had both photophobia and phonophobia, and 55.3% of patients (42/76) had associated nausea. Only 2.6% (2/76) of patients had vomiting

### Past history of headache

Previous history of primary headache disorders was seen in 36.8% (28/76) of patients. Moreover, 23.7% (18/76) had history of migraine without aura, while 13.1% (10/76) had tension- type headache. In 18 patients who had history of migraine, 14 (77.8%) had headache attacks which was similar to previous migraine attacks, while 4 had headache which was mild and different in character compared to previous migraine attacks.

### Comparison between COVID-19-infected patients with and without headaches

A comparison between COVID-19-infected patients with and without headaches showed that those with headaches were significantly younger than those without headaches (48.89 vs 54.61 years; $p < 0.007$). Females were more common in the headache group (53.9% vs 27.5%; $p < 0.001$). There was no difference in the presence of systemic symptoms like fever, cough, breathlessness, vomiting and diarrhoea between both groups. Sore throat, anosmia and myalgia were more common in those with headaches. There was no difference between the groups with respect to the presence of diabetes, hypertension, hypothyroidism, chronic kidney disease, chronic liver disease, bronchial asthma, stroke, epilepsy and Parkinson's disease. Most patients with a history of migraine and tension-type headache were in the headache group ($p < 0.001$). Inflammatory markers like leukocyte count ($p < 0.017$,) ESR ($p < 0.023$) and ferritin ($p < 0.014$) were higher in patients without headache (Table 1).

## Discussion

Headache appears to be an important symptom of COVID-19 infection and can occur as an inaugural and isolated symptom, heralding other systemic and neurological manifestations. SARS-CoV-2 is a neurotrophic virus and gains entry into the cells using the angiotensin-converting enzyme-2 (ACE2) receptor on the surface of the cells. It has been hypothesized that the virus reaches the nervous system either through a haematogenous spread due to a leaky blood–brain barrier or like a 'Trojan horse' through infected lymphocytes.[1,8] It is postulated that SARS-CoV-2 virus can also gain direct entry into the central nervous system through the cribriform plate or the trigeminal nerve endings, resulting in various neurological manifestations.[1,8]

The incidence of headache in various studies ranged from 6.5% to 71%.[4] A recent meta-analysis of multiple studies showed a pooled prevalence of headache to be 14.7% (95% CI, 10.4–18.9).[2] While most studies from around the world demonstrate a higher prevalence of CRH,[7,9,10] published literature from Asia shows a much lower prevalence of 6%–34%.[3] Another small study of 21 COVID-19 patients from India showed a headache prevalence of 13.6% only.[11] This is probably because most early studies from Asia were retrospective chart reviews, while studies from other countries were prospective involving a larger number of patients.

In this study, we found that COVID-19 patients with headaches were younger when compared to those without headaches. Headaches were also more common in females, although COVID-19 infection was seen more commonly in males. Female preponderance in CRH was also seen in other studies, corresponding to an increased incidence of primary headache disorders like migraine in females.[7,9,10]

CRHs according to the ICHD3 can be classified under acute headache attributed to systemic viral infection (9.2.2.1).[5] These headaches, as defined, occur in temporal relation to the onset of viral infection and worsen or improve parallel to the course of the disease. Headache is either diffuse in character or of moderate to severe in intensity. In this study, the majority of patients described a bifrontal or holocranial headache with a dull aching or throbbing quality, similar to the observations from other studies.[4,7,9,12] However, when analysing the

**Table 1.** Comparison of COVID-19-infected patients with and without headaches.

| Variable | COVID-19 with headache (n = 76) | COVID-19 without headache (n = 149) | P value |
|---|---|---|---|
| Mean age in years (SD) | 48.89 ± 15.19 | 54.61 ± 14.57 | 0.007 |
| Gender | | | |
| Male | 35 (46%) | 108 (72.4%) | 0.001 |
| Female | 41 (53.9%) | 41 (27.5%) | 0.001 |
| Associated symptoms | | | |
| Cough | 47 (61.8%) | 92 (61.7%) | 0.9 |
| Dyspnoea | 31 (40.7%) | 58 (38.9%) | 0.78 |
| Fever | 48 (63.1%) | 78 (53.4%) | 0.12 |
| Sore throat | 14 (18.4%) | 10 (6.8%) | 0.007 |
| Anosmia/ageusia | 6 (7.9%) | 3 (2.1%) | 0.03 |
| Myalgia | 19 (25%) | 15 (10.3%) | 0.003 |
| Vomiting | 2 (2.6%) | 5 (3.4%) | 0.76 |
| Diarrhoea | 6 (7.9%) | 9 (6.2%) | 0.59 |
| Confusion | 1 (1.3%) | 4 (2.7%) | 0.510 |
| Co-morbid conditions | | | |
| Diabetes | 36 (47.3%) | 75 (50.3%) | 0.674 |
| Hypertension | 29 (38.2%) | 72 (48.3%) | 0.147 |
| Coronary artery disease | 2 (2.6%) | 15 (10.1%) | 0.046 |
| Chronic kidney disease | 2 (2.6%) | 6 (4.02%) | 0.593 |
| Bronchial asthma | 2 (2.6%) | 2 (1%) | 0.489 |
| Hypothyroid | 2 (2.6%) | 3 (2.1%) | 0.766 |
| Stroke | 1 (1.3%) | 5 (3.4%) | 0.369 |
| Parkinson's disease | 0 (0) | 3 (2.01%) | 0.213 |
| Chronic liver disease | 0 | 2 (1.4%) | 0.310 |
| Epilepsy | 1 (1.3%) | 1 (0.7%) | 0.626 |
| Past history of migraine/TTH | | | |
| Migraine | 18 (23.7%) | 1 (0.7%) | 0.001 |
| TTH | 10 (13.2%) | 2 (1.4%) | 0.007 |
| Investigations | | | |
| Haemoglobin (12–16 g/dL) | 13.10 ± 2.08 | 13.30 ± 2.49 | 0.561 |
| Total count (4–11 × $10^3$/μL) | 7234.17 ± 3054.96 | 8773.35 ± 5103.65 | 0.017 |
| Platelet count (150–400 × $10^3$/μL) | 161.08 ± 107.00 | 244.23 ± 413.03 | 0.088 |
| Erythrocyte sedimentation rate (10–20 mm/h) | 39.28 ± 23.29 | 50.41 ± 27.61 | 0.023 |
| Creatinine (0.57–1.11 mg/dL) | 1.26 ± .893 | 1.93 ± 7.77 | 0.464 |
| Sodium (136–145 mEq/L) | 136.12 ± 3.69 | 135.07 ± 4.11 | 0.068 |
| C-reactive protein (0.02–0.5 mg/dL) | 9.08 ± 23.17 | 8.11 ± 7.70 | 0.653 |
| Ferritin (4.6–204 ng/mL) | 381.06 ± 485.27 | 657.10 ± 863.80 | 0.014 |
| D-dimer (0.0–255 ng/mL) | 464.89 ± 860.31 | 767.96 ± 1294.79 | 0.072 |
| Random blood sugar (<200 mg/dL) | 190.05 ± 81.69 | 197.82 ± 75.68 | 0.597 |

COVID: coronavirus disease; SD: standard deviation; TTH: Tension-type headache.

intensity of pain, we found that the majority of our patients had a headache of mild to moderate intensity. Data from across the world suggest that CRHs are of moderate to severe intensity.[4,10,12] In our headache cohort, the majority had short-lived headaches lasting less than 5 days, while few had headaches beyond 10 days. A proportion of COVID-19-infected patients can have headaches lasting beyond 6 weeks of their illness, as observed in a study from Spain.[9] These discrepancies may be due to differences in various host factors and viral strains, specific to our population.

We also observed that patients with a history of migraine and tension-type headache were more likely to have CRH. But the majority of patients with CRH had no past history of primary headaches, in line with the observation from published literature,[4,7,12] suggesting that COVID-19 infection per se may be the cause of the headache. CRH in patients with migraine are reported to have a rapid onset, longer duration, higher intensity and poor responsiveness to analgesic medication.[4,7,9] However, we found that the majority of our patients with migraine and CRH had attacks of similar nature

as their previous migraine episodes, and in only a few, headache had a different character. Previous studies have described anosmia, ageusia, loss of appetite, weight loss and diarrhoea as distinctive features of CRH.[4,7,12] In thus study, the majority of patients with headache did not have anosmia, although anosmia was more common in the CRH group. Anosmia reflects SARS-CoV-2-induced olfactory epithelial cell damage rather than olfactory neuronal injury[13] and thus may be a marker for COVID-19 infection rather than headache. We did not find any association of headache with loss of appetite, weight loss or diarrhoea. These discrepancies in various clinical features may be due to genomic variations in the host and virus strains. Genomic variations involving the ACE2 receptor, like rs2285666 polymorphisms, are reported in the Indian population.[14]

We also observed dissociation between inflammatory markers and the presence of headache. A negative correlation between inflammatory markers and headache was also observed in another study, where interleukin-6 (IL-6) levels were lower (22.9 (57.5) vs 57.0 (78.6) pg/mL; $p=0.036$) in those with headaches.[9] These findings suggest that direct activation of the trigeminovascular system by SARS-CoV-2 through the trigeminal nerve endings in the nasopharyngeal cavity may be an important mechanism of CRH, rather than systemic inflammation.[7,9,12]

Many of the patients with CRH, even those without a history of migraine, had associated photophobia and phonophobia. The exact mechanism by which a migraine-like headache is triggered by a systemic viral infection is not known. Calcitonin gene–related peptide (CGRP) is a 37-amino-acid neuropeptide known to play a key role in migraine pathogenesis.[15] There is a co-existence of CGRP and ACE2 receptors in the neurons of trigeminal ganglia.[4,16] Inflammatory cytokines like tumour necrosis factor-alpha (TNF-alpha) and IL-6 are also known to increase CGRP levels.[17] Studies in the rat trigeminal ganglion neurons have demonstrated that TNFR1 receptors are present in the majority of CGRP-containing neurons and there is an increase in CGRP secretion and CGRP promoter activity when cultures are treated with TNF-alpha.[18] These findings suggest that the invasion of trigeminal nerve endings by SARS-CoV2, along with an increase in the inflammatory cytokines, ultimately causes an increase in CGRP levels, producing an activation of trigeminovascular system, resulting in a migraine-like headache.[17]

The main limitations of this study include the observational nature, hospital setting, limited number of patients and lack of propensity-matched cohorts. Hence, we cannot extrapolate the findings of this study to the general population. The questionnaire was neither validated nor pilot tested prior to the study as we had limited time and resources during the peak of the pandemic. However, it is one of the largest studies on CRHs from the Indian subcontinent. Another strength of this study is that we have compared the group with headaches with those without headaches. We have also attempted to hypothesize plausible mechanisms for CRHs.

## Conclusion

Headaches are a common and early symptom of SARS-CoV-2 virus infection in the Indian population. CRH is more frequently seen in young females and in those with a history of primary headache disorders like migraine and tension-type headache. These headaches usually have a dull aching quality and are mild to moderate in intensity. They are usually benign and short-lived. The lower level of inflammatory markers in those with headaches suggests that these headaches are probably related to the local spread of SARS-CoV-2 virus through the trigeminal nerve endings and ultimately result in the activation of the trigeminovascular system.

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### Consent for publication

Each patient provided informed consent for publication

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

### Ethical approval

Ethical approval for this study was obtained from the Institutional Review Board of St. John's Medical College Hospital, Bengaluru, India (IEC Study Ref No.358/2020).

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### Informed consent

Written informed consent was obtained from all subjects before the study.

### IRB approval

The study was approved by the Institutional Review Board of St. John's Medical College Hospital, Bengaluru, India.

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### Supplemental material

Supplemental material for this article is available online.

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