

## Brief Communications

### Case Series of Headache Characteristics in COVID-19: Headache Can Be an Isolated Symptom

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Headache was reported in up to one-third of the hospitalized patients; yet, the clinical characteristics of headache associated with coronavirus disease 2019 (COVID-19) have not been defined. This observational case study included patients who were consulted to headache unit due to headache and had COVID-19 illness. Headache features in 13 PCR-confirmed COVID-19 patients with mild symptoms were reported. Headache was the isolated symptom of the COVID-19 in 3 patients and emerged as an early symptom during the disease course in all patients. Patients specified severe, rapid onset, unrelenting headache with migraine-like features, as well as unusual sensory symptoms such as anosmia, and gastrointestinal symptoms such as diarrhea and loss of appetite and weight. Headache lasted up to 3 days in 70% of the patients and resolved in all patients within 2 weeks. Despite the fact that most of the patients were female and headache characteristics were suggestive of migraine, majority of patients were not suffering from primary headaches. It was concluded that headache could be an isolated symptom of COVID-19, which might possibly be ignored in asymptomatic patients. Headaches associated with COVID-19 included features resembling migraine and/or atypical symptoms including anosmia and diarrhea.

**Key words:** headache, coronavirus disease 2019, migraine, gastrointestinal symptoms, calcitonin gene-related peptide, cytokines

(*Headache* 2020;60:1788-1792)

Coronavirus disease 2019 (COVID-19), caused by a novel coronavirus called SARS-CoV-2, was initially characterized by respiratory system manifestations.<sup>1-3</sup> Yet, manifestations of the nervous system such as headache, dizziness, anosmia, ageusia, and loss of appetite have been recognized during the COVID-19 pandemic. SARS-CoV-2 uses the transmembrane ACE2 receptor to enter the mammalian host cells. The ACE2 receptor was detected in various cells in humans including the airway lung epithelial cells,

vascular endothelial, pericytes, and smooth muscle cells, and neuronal cells in the trigeminal ganglia, olfactory bulb, and other cortical and subcortical areas.<sup>3,4</sup> Viral neuroinvasion is proposed to occur through synaptic transmission from infected cells, brain penetrance via olfactory groove, or perivascular lymphocytic infiltration. Understanding the mechanisms of neurological symptoms including headache and means for neuroinvasion is an important step to develop management strategies for the disease. In a similar manner providing the diagnostic descriptions of wide range of COVID-19 manifestations other than the respiratory system is critical for early diagnosis, isolation, and treatment.

The accessible studies do not report headache features in patients with COVID-19, except those including case presentations and general characteristics.<sup>1-3,5-9</sup>

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Accepted for publication June 22, 2020.

*Conflict of Interest:* None

Headache was reported as low as 6.5% at the onset of the disease in hospitalized patients but could be as high as 71% in the questionnaire among health care workers.<sup>3,5-9</sup> Interestingly, a clinical observation suggested that headache may be more prevalent in patients having gastrointestinal symptoms.<sup>8</sup> Though headache attributed to a systemic viral infection, without meningitis or encephalitis is classified in the ICHD-3,<sup>10</sup> detailed clinical manifestations other than diffuse pain and moderate to severe intensity are needed to be defined to develop diagnostic criteria of COVID-19 headache during the pandemic.

### CASE PRESENTATIONS

We reported a case series of 13 patients who were diagnosed with mild COVID-19 and having a chief complaint of headache. Observational study included patients who were consulted to headache unit due to headache and had PCR-confirmed COVID-19 illness during April 15-May 15, 2020. Headache features and associated symptoms were questioned by a headache specialist. The neurological symptoms and signs of viral meningoencephalitis were absent. None of the patients described runny nose or symptoms of nasal congestion that were easily recognizable in viral respiratory diseases. The important headache characteristics are summarized in Table 1. Patients had no comorbid diseases, except Case 4 and Case 7 who had hypertension and diabetes. The mean age of the patients was relatively young,  $40.2 \pm 11$ , possibly due to the lockdown restriction on people aged 65 and over, and those under 20. Though, majority of patients were female (9 out of 13), only 5 out of 13 were diagnosed with migraine, and 1 had rare tension-type headache (TTH) attacks. Seven out of 13 patients were not suffering from any prior headaches.

All patients noticed that the headache was distressful and/or different from previous attacks. Headache was mostly described as moderate to severe intensity and incapacitating. Headache was almost exclusively described as throbbing and/or pressing in nature, and aggravated with routine movements and bending over. Headache was holocranial with a particular focus in bilateral frontal and temporal areas. Nine patients used analgesics, mainly paracetamol or NSAIDs and reported partial response or temporary

recovery lasting hours. Headache was resolved within 3 days in 70% of the patients and no persistent headache was observed. The course of the headache was variable usually depending on the active phase of the disease. However, in some patients, headache symptoms began following diarrhea, lasted 24 hours, and were replaced with other symptoms (Case 7). In contrast, in Case 3, the new headache associated with COVID-19 continued 2 weeks throughout the course of the PCR positivity.

Photophobia and/or phonophobia were the most frequent associated symptoms (9/13), and patients with previous migraine attacks described the nature of these associated symptoms as very disturbing (Cases 1 and 6). Osmophobia, a typical migraine associate was reported by a non-headache sufferer, along with photophobia and nausea during the COVID-19-associated severe throbbing headache (Case 3), or was described as severely disturbing by a migraine patient (Case 8). Moreover, anosmia was reported with photophobia and/or phonophobia by 2 patients (Table 1).

Five out of 13 patients diagnosed with COVID-19 headache reported gastrointestinal symptoms of diarrhea, loss of appetite, or weight loss, which were not typically associated with primary headaches.

Intriguingly, we also observed headache as an isolated symptom of COVID-19 in 3 patients who were detected during the screening of filiation teams (Table 1). In that regard, our Case 12 needs emphasis because he was a neurology resident who paid particular attention to his symptoms. As a rare TTH sufferer, he first noticed the unusual features of his headache such as acute onset, severe intensity, throbbing nature superimposed with stabbing pain, worsened with movements, and failed to respond to paracetamol. He was diagnosed with COVID-19 on the third day of the headache. The headache was the only complaint that emerged within 48 hours following the contact with the index case and other common COVID-19 symptoms, such as fever, cough, sore throat, or gastrointestinal symptoms, were absent.

### DISCUSSION

Headache was seen during the early course of the disease in all patients. As being one of the initial symptoms and early manifestation of the disease, headache seems not to be necessarily associated with the disease

Table 1.—Demographic Features and Headache Characteristics of Mild Symptomatic COVID-19 Patients

Case No	Age Sex	Previous Headaches	Headache				Associated Symptoms		
			Onset	Localization	Duration	Quality	NRS	Sensory	Gastrointestinal & Others
1	38 F	Rare migraine like	Second day, following fever & cough	Bilateral fronto-temporal	48 hours	Throbbing, worsens with movements	7	Photophobia	Nausea
2	54 F	Migraine diagnosis	Within 24 hours following fever, anosmia and diarrhea	Bilateral fronto-temporal	10 days	Throbbing, worsens with movements	9	Photophobia	Nausea
3	35 F	None	Within 24 hours following sore throat and diarrhea	Bilateral occipital & vertex	14 days	Throbbing	9	Photophobia	Nausea
4	52 M	None	Second day following fever & cough	Diffuse	24 hours	Pressuring	4	Osmophobia	Diarrhea
5	44 F	None	First day	Vertex	7 days	Pressuring	5	None	None
6	34 F	None	First day following cough, fatigue and myalgia	Bilateral fronto-temporal	24 hours	Pressuring, pulsatile with movements	6	Photophobia	None
7	61 M	None	Second day following fever, diarrhea & dizziness	Bilateral fronto-temporal	24 hours	Pressuring	5	None	Nausea
8	26 F	Migraine diagnosis	Second day, following fever, diarrhea & dyspnea	Diffuse	24 hours	Throbbing	8	Osmophobia	Diarrhea
9	43 M	None	Fourth day, following fever, anosmia & dyspnea	Bilateral fronto-parietal	48 hours	Pressuring & throbbing, worsens with movements	4	Photophobia, Anosmia	Dizziness
10	26 F	Migraine diagnosis	First day following sore throat	Bilateral, fronto-parietal	4 days	Throbbing, worsens with movements	8	Photophobia	Nausea
11	41 F	None	Isolated symptom of COVID-19	Bilateral, frontal to occipital	60 hours	Pressuring, worsens with movements	10	Photophobia	Diarrhea
12	26 M	Rare tension type	Isolated symptom of COVID-19	Bilateral, frontal vertex	3 days	Throbbing, rare stabbing, worsens with movements	8	Photophobia	Nausea
13	43 F	Migraine diagnosis	Isolated symptom of COVID-19	Bilateral, fronto-temporal	3 days	Throbbing, worsens with movements	10	Photophobia	Vomiting

NRS = Numeric Rating Scale.

severity during the progression of the disease including lung involvement and vascular complications.<sup>3</sup> Yet, the headache had some similarities to migraine attacks, primary headache sufferers specified different features from their usual headaches such as higher intensity, rapid course, and resistance to usual analgesic medication during the disease course. It is essential to point out that symptoms associated with migraine may primarily have a central origin whereas symptoms associated with COVID-19 headache are more probably related to the peripheral mechanisms of infection.

A peculiar feature of COVID-19 headache in some patients was significant weight loss (5 kg within 3 days) associated with headache. The weight loss could not be accounted by diarrhea, lasting a day or loss of appetite, and suggested that increased catabolism mediated by COVID-19 induced cytokines and cortisol was likely involved in the process. We think the rapid weight loss with significantly reduced appetite could also be a distinctive feature for the COVID-19 headache. The headache had migraine-like features such as throbbing quality, aggravation by routine movements, sensory disturbances such as photophobia and phonophobia, nausea. Headache recovery within 3 days in 9 patients was remarkable as being consistent with the duration of migraine headache. However, the headache had several characteristics that were not associated with migraine. The clinical features of headache associated with COVID-19 are listed in Table 2, yet reported cases were limited to highly selected patients.

It seems implausible to explain the early and solely manifestation of the headache in isolated

cases through indirect effects of virus via circulating inflammatory mediators leading to cytokine storm, viremia, endothelial and vascular invasion, metabolic derangement, or hypoxic damage.<sup>3</sup> Rather, headache is likely due to the direct invasion of trigeminal nerve ending by SARS CoV2 in the nasopharyngeal cavity, leading to the activation of the trigeminovascular system. Co-existence of calcitonin gene-related peptide (CGRP) with angiotensin system in small- and medium-sized sensory neurons and trigeminal ganglia suggests that early activation of trigeminal nerve endings by the virus could initiate well-known mechanisms that result in migraine-like headache.<sup>3</sup> The correlation of circulating CGRP and pro-inflammatory cytokine interleukin-6 levels postulates a possible mechanism of headache in the later stage of the COVID-19 illness.<sup>3,11</sup>

Understanding the underlying mechanisms of anosmia symptom associated with COVID-19 patients may be helpful to elucidate neuroinvasive processes of SARS-CoV-2. While the SARS-CoV-1 and MERS-CoV have been shown to invade the central nervous system via transsynaptic spread in transgenic mice models,<sup>12</sup> it is unclear whether SARS-CoV-2 penetrates brain similarly through olfactory tract. Available studies revealed that ACE2 was expressed in the olfactory epithelium but not in the olfactory sensory neurons. Thus, the clinical anosmia is probably due to SARS-CoV-2-induced olfactory epithelial cell damage rather than olfactory neuronal injury.<sup>13,14</sup>

Recent brain imaging data suggested brain involvement in a COVID-19 patient with anosmia by demonstrating hyperintensity in the gyrus rectus and olfactory bulb.<sup>15</sup> It is not clear whether such cortical signal change in the olfactory area can be attributed to the direct neuroinvasion. However, the case shows the involvement of the cerebral cortex relevant to clinical anosmia, which is a common symptom of COVID-19.

**Table 2.—Headache Associated With COVID-19 Shows Unusual and/or Migraine-Like Various Features**

Unusual	Migraine-Like
New unrelenting headache	Moderate-severe pain intensity
Rapid/gradual onset	Fronto-temporal location
Bilateral/diffuse	Resolution in 72 hours
Pressing quality	Pulsating quality
No prior headache history	Aggravation by activity
Anosmia/ageusia	Photophobia
Diarrhea	Phonophobia
Loss of appetite	Osmophobia
Weight loss	Nausea

## CONCLUSION

We concluded that headache is one of the earliest symptoms of the COVID-19 and could be an isolated feature of the illness. Evaluation of the patients admitted to the medical facilities with headache according to the headache features described in the presented cases with COVID-19 would provide early isolation

and treatment of the cases during the pandemic. The complex interaction of COVID-19 pathophysiology with migraine including angiotensin system, CGRP, inflammatory cytokines, and trigeminovascular activation needs to be investigated with further basic and clinical studies.

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