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## Case Report

# The unusual course of a migraine attack during COVID-19 infection – Case studies of three patients

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## ABSTRACT

The effect of the coronavirus disease 2019 (COVID-19) on the nervous system remains undefined. Some studies have shown that headache is one of the most common symptoms and often the first neurological symptom in patients with confirmed infection. There are only a few reports concerning the effects of COVID-19 on the course of migraine.

This article investigates three female patients with prolonged history of migraine, in which atypical phenomenology and course of migraine attacks were observed during COVID-19 infection.

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## Introduction

The coronavirus disease (COVID-19) which emerged in Wuhan, China in November 2019 has become a global pandemic [1]. Although understanding of this disease entity and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus itself which causes it is growing, the mechanism of the development of neurological symptoms in COVID-19 is still unknown [2]. It seems that the emergence of neurological symptoms occurs through three possible mechanisms: direct involvement of the nervous system, immune-mediated post-inflammatory complications, and a mechanism secondary to lung damage and systemic disease [3,4].

Although the main symptoms of COVID-19 are fever, cough and shortness of breath, one of the most frequently observed symptoms preceding or occurring during and after SARS-CoV2 infection is headache [5,6]. Most often, this is phenotypically similar to tension type headache and is described as a pressing or distressing pain, bilateral and difficult to treat. There are few reports concerning the effects of COVID-19 on the course of migraine [7].

This article presents three patients suffering from migraine over many years, in which atypical phenomenology and course of migraine attacks were observed during COVID-19 infection.

## Case reports

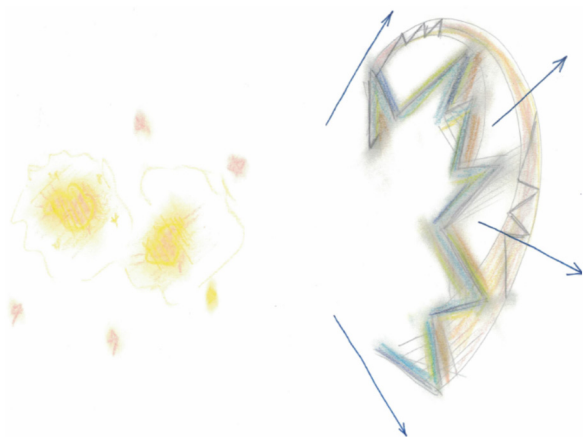
## Case 1

This 45-year-old female had experienced episodic migraines, without aura or photophobia, since she was 26 years old. Consistently, her migraine attacks occurred about twice a month with a good response to triptans or paracetamol. In September 2020, the first visual aura appeared in both left visual fields along with olfactory hypersensitivity. She experienced a geometric shape within the peripheral visual field that continued to enlarge proximally; ultimately leading to severely obscured vision. The visual disturbance was grey and dark green in colour and gradually dissipated, lasting about 35 min. Subsequently, she experienced the most severe migraine headache in her life with simultaneous photophobia which did not respond to typical pain medication. Brain MRI and angio-MRI were performed and showed no abnormalities. After 2 days, the headache disappeared and then the patient lost her sense of smell. She developed a fever and severe muscle pain. A PCR (polymerase chain reaction) test for COVID-19 was positive, confirming infection. After the infection, aura with or without migraine headache did not occur again.

## Case 2

This 24-year-old female had suffered from episodic migraines without aura or photophobia since she was 16 years old. Her migraine attacks appear approximately once a month with a good response to nonsteroidal anti-inflammatory drugs and paracetamol. In September 2020 there was a sudden, paroxysmal stinging

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**Fig. 1.** The aura vision drawn by the patient. The arrows show the direction in which a coloured rainbow enlarging and appeared in the outer field of vision.

and burning sensation in her ears with transient hearing impairment. The symptoms were accompanied by a visual aura in both right visual fields that lasted 20 min. The patient described these two as white spots and disco lights that lasted for a few minutes and then a colourful, curved, enlarging rainbow appeared in the outer field of vision, which eventually covered the entire field of vision in that eye (Fig. 1). After the visual aura had subsided, very severe migraine pain with photophobia and nausea occurred, which provoked status migrainosus. The patient required hospitalisation and a brain MRI was performed which showed no abnormalities. Two days after the migraine condition stabilised, the patient lost her sense of smell and developed a dry cough. A PCR test for COVID-19 was positive. After the infection, the migraine with aura or aura without headache did not occur again.

### Case 3

This 52-year-old patient presented with a history of suffering from chronic migraine without aura from when she was 45 years old. She is treated prophylactically with topiramate. Her migraine headache occurs approximately nine days a month, no visual auras have ever occurred. In August 2020, she experienced anosmia, muscle aches, fever and a dry cough. A PCR test for COVID-19 was positive. During the infection, she developed a visual aura without headache three times within a week. The patient described this as flashes of light and various movements of images in the visual field, she described these as coloured lines bending inward and jumping grey zigzags. The entire field of vision was not covered. The visual symptoms disappeared after approximately 15–30 min.

### Discussion

The effect of COVID-19 on the nervous system and the mechanisms of neurologically related symptoms present in patients with COVID-19 remain undefined. Several possible routes for the spread of the SARS-CoV-2 virus in the human body are currently postulated: use of the bloodstream with subsequent neuronal dissemination, infection of endothelial cells within the blood-brain barrier or blood-cerebrospinal fluid barrier, use of trans-synaptic pathways after infection of the endings of nerves (forward or retrograde transport) mainly in the olfactory bulb, crossing the blood-brain barrier as a result of infection of leukocytes or through the use of the glymphatic system [8–10]. However, it seems that the most likely receptor mechanism is the use of angiotensin-converting enzyme type 2 (ACE2) to break the blood-brain barrier. ACE2 expression outside the lung tissue has been confirmed in neu-

rons, astrocytes, oligodendrocytes, the olfactory bulb, substantia nigra, the brainstem and posterior cingulate cortex [3,8]. SARS-CoV-2 has been shown to be a neurotrophic virus that has the ability to infect and replicate in cultures of neuronal cells and the brain. In postmortem examinations, virus RNA has been detected in the brain in about 30–40% of cases [8,11].

Some studies have shown that headache is one of the most common and often the first neurological symptom in patients with confirmed infection. According to various studies, the incidence of headaches varies and is within a wide range: 10–70% [1,12,13]. Typical coronavirus induced headaches frequently appear to be bilateral, pulsating, pressing, stabbing, dull and demonstrate analgesic resistance [14,15]. The mechanism by which headache occurs in COVID-19 remains unclear. It can be postulated that it is similar to the mechanisms observed in other respiratory viruses, such as influenza A and B, where headache is often accompanied by fever and fatigue. The criteria for headache caused by viral infection are precisely defined in the third edition of the International Classification of Headaches, according to which, besides temporal association with viral infection, headache is characterised by diffuse pain of moderate to severe intensity [16]. Some authors suggest that headache during COVID-19 may be a consequence of direct involvement of the trigeminovascular structures in the ACE2 receptor mechanism [17].

All our patients were diagnosed as suffering from migraine without aura for many years [16] and did not have any other chronic comorbidities, e.g. hypertension, diabetes mellitus, and were not taking any medications other than those used for migraines. There were also no previous incidents of blindness, visual impairment or other ophthalmic disorders. After COVID-19 infection, each of these patients had an ophthalmological consultation, an ultrasound examination of the cerebral arteries and brain MRI, which did not reveal any abnormalities.

The link between visual aura and COVID-19 infection was significant in all cases. In two patients, the first migraine attack with aura was probably the first symptom of infection. In the third, visual auras appeared simultaneously with other symptoms typical of COVID-19. Interestingly, in all these patients, apart from the unusual course of the migraine attack, olfactory phenomena occurred: in one of them there was initial olfactory hypersensitivity and in all of them an eventual loss of smell. None of them had experienced sensory hypersensitivity prior to migraine attacks.

In such cases, it is important to carry out a detailed differential diagnosis to exclude other causes of visual disturbances, such as retinal ischemia or detachment, temporal arteritis, transient ischemic attack (TIA), carotid dissection or optic neuropathy [18]. In particular, attention should be paid to TIA with blurred vision, given the already known pro-thrombotic properties of the SARS-CoV2 virus [19].

Migraine without aura is the most common form of migraine and occurs in approximately 80% of migraineurs. In the case of migraine with aura, which affects about 20% of patients, it should be remembered that according to the criteria of diagnosis, the patient must have at least two such attacks to be able to recognize migraine with aura [16]. The visual aura is associated with cortical spreading depression (CSD) from the visual cortex to the primary somatosensory and motor cortex. Sometimes CSD is not a strong enough trigger to trigger a headache after a migraine aura. In such cases, we recognize an aura without a headache [7,16,20]. However, on the basis of numerous clinical observations, it can be assumed that the frequency of aura in patients diagnosed with migraine without aura is higher than is generally assumed. Further research is required to obtain accurate observations and determine the prevalence of this phenomenon.

The cases presented in this report may suggest that coronavirus may affect the bioelectrical activity of the brain and perhaps –

by increasing activity, especially in the occipital lobes – it may be responsible for CSD and successive appearance of aura. The mechanism of this phenomenon remains unknown. These observations require confirmation in larger groups of patients and with the use of functional imaging techniques. To the best of our knowledge, this is the first report in the world literature regarding the association of migraine aura with COVID-19.

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### Competing interests

None declared.

### Ethical approval

Approval for this research was given by the Commission of Ethics at the Wrocław Medical University.

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