Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in January 2020 as the cause of a viral pneumonia epidemic in Wuhan, China. Due to its rapid spread, it became a worldwide threat in a very short period of time (1). In March 2020 the WHO declared a pandemic of coronavirus disease 2019 (COVID-19) (2). Infection with other coronaviruses typically causes respiratory symptoms (1). In contrast, COVID-19 infection damages multiple body organs. Although the most frequent manifestations include respiratory tract symptoms (cough, loss of smell and taste), COVID-19 may also cause central nervous system (CNS) damage, renal injury, cardiological and haematological symptoms (3). In May 2020, 2 months after the beginning of the pandemic, our group published a report of the novel skin manifestation of COVID-19 (4), which was the first to report cutaneous hyperaesthesia in patients with SARS-CoV-2 infection. To date, after 5 months, no additional data has been published, and very little is known about the prevalence of this phenomenon. We believe that cutaneous hyperaesthesia remains a very rare clinical manifestation of COVID-19; nevertheless, it is not unique, and there are increasing reports of this manifestation.

MATERIALS AND METHODS

In the 5 months since reporting this novel manifestation of COVID-19 (4), the authors have been contacted by several patients and/or their family members from around the world reporting similar symptoms. All patient data pertaining to the similarities and differences between subjects with skin sensitivity due to COVID-19 were collected. Each patient was also asked additional questions, with particular focus on additional dermatological symptoms that could have caused the above-mentioned hypersensitivity. Moreover, alleviating factors, medication, and duration of hyperaesthesia were taken in account.

RESULTS

In total, this study collected data from 9 COVID-19 patients (4 women, 5 men, mean ± standard deviation age 47.7 ± 8.1 years) with cutaneous hyperaesthesia. The majority of the patients (6 people; 66.7%) presented typical general symptoms of COVID-19 (fever, malaise or dry cough) and only 2 reported associated dermatological manifestation. In both of those cases this was an itchy exanthema; however, in one of these patients this could have developed as a possible allergic reaction to paracetamol. Most frequently, hyperaesthesia appeared with, or directly after, the onset of general symptoms of COVID-19 (2–3 days); however, in one patient it was the first sign of the infection. Moreover, one of the patients reported increased sensitivity of the skin 5 days after the resolution of general COVID-19 symptoms. The duration of hyperaesthesia varied considerably among subjects (from 1 day to 6 months). The treatments applied were not similar between patients; 2 subjects were treated with hydroxychloroquine and 2 with symptomatic treatment (including acetylsalicylate and metamizole). Only 2 (22.2%) were treated for cutaneous hyperaesthesia (gabapentin/duloxetine and diclofenac injections). Among alleviating factors, patients most frequently reported oral, anti-inflammatory medication (22.2%) and warm baths (22.2%) (Table 1).

Table 1. Patients’ clinical characteristics

| Pat. No. | Sex (F/M) | Age, years | Timing of hyperaesthesia | Duration of hyperaesthesia | Additional symptoms | Additional dermatological symptoms | Treatment | Alleviating factors |
|---------|----------|------------|--------------------------|---------------------------|---------------------|----------------------------------|-----------|-------------------|
| 1       | F 40     | With general symptoms | 10 days                  | Fever, dry cough           | Itchy, scaly exanthema | Hydroxychloroquine                | Diclofenac p.o. |
| 2       | M 40     | With general symptoms | 10 days                  | Fever, general malaise     | None                | Hydroxychloroquine               | Gabapentin and duloxetine |
| 3       | M 44     | 5 days after resolution of general symptoms | 6 months                  | Asymptomatic               | None                | None                             | None          |
| 4       | F 62     | 14th day of general symptoms | No data                   | No data                    | No data             | Diclofenac injections             | None          |
| 5       | F 62     | 2nd day before general symptoms | 24 h                      | Fever, myalgia and fatigue | None                | ASA p.o.                         | ASA p.o.           |
| 6       | M 49     | 4th day of general symptoms | 6 days                    | Fever, dry cough, fatigue, Burning sensation in nose, anosmia | None                | None                             | None          |
| 7       | M 49     | No data | No data                   | Fever, dry cough, fatigue, Burning sensation in nose, anosmia | None                | None                             | None          |
| 8       | F 57     | 3rd day of general symptoms | 10 days                   | Fever, fatigue,            | Itchy exanthema      | Metamizole                        | Warm baths         |
| 9       | M 42     | 3rd day of general symptoms | 3rd day, still present    | Fever, fatigue, headache   | None                | Paracetamol, ASA p.o.             | NSAID           |

F: female; M: male; p.o.: per os (by mouth); ASA: acetylsalicylic acid; NSAID: non-steroidal anti-inflammatory drug.
DISCUSSION

Neurological manifestations and complications are being frequently reported in COVID-19 patients. The mechanism of CNS and nerve damage is currently unknown; however, authors indicate a possible role of angiotensin-converting enzyme 2 (ACE2) receptors (found in glial cells and spinal neurones), disruption of the blood-brain barrier during viraemia, or invasion of peripheral nerve terminals (4). Although the most common neurological symptoms associated with SARS-CoV-2 infection are dizziness, headache, impaired consciousness and agitation, there may be also severe complications, including ischaemic or haemorrhagic stroke or encephalopathy (4–6). Subjective neurological symptoms (SNs) are common symptoms of COVID-19 and, according to Liguori et al. (7), may be present in up to 91% of subjects. The most commonly reported are hyposmia (38.8%) and dysgeusia (46.6%). Moreover, the authors found that some of the symptoms (sleep impairment, loss of smell and taste or headache) are significantly more common among female patients (8).

Cutaneous hyperaesthesia is a SNs, and is defined as an increased sensitivity to stimulation (8). Although frequent in primarily neurotropic viruses (e.g. herpes viruses) (9) it is a very rare manifestation of SARS-CoV-2 infection (10). Pain is an important problem in symptomatic patients with COVID-19, but the exact pathogenesis is unknown. Primary reports suggested that ACE2 receptor present in sensory neurones may play an important role in the uptake of SARS-CoV-2 and development of neurological effects (including nerve pain) (11). Interestingly, according to Moutal et al. (11), SARS-CoV-2 spike protein may decrease the pro-nociceptive signalling of vascular endothelial growth factor-A (VEGF-A) and act as an analgesic factor. It was demonstrated that VEGF may promote mechanical allodynia and thermal hyperalgesia; however, when blocked, these symptoms decrease significantly. Moreover, the authors raised the possibility that pain in COVID-19 may be diminished by spike protein, but did not exclude that other viral proteins may be pro-nociceptive (11). Nevertheless, it must be emphasized that antibodies targeting VEGF- binding site of neuropilin-1 may cause neuropathy due to splicing of a neuroprotective isoform of VEGF-A (12).

In conclusion, further research is needed to determine the prevalence of cutaneous hyperaesthesia in COVID-19 patients and to clarify the pathogenesis of this symptom.

The authors have no conflicts of interest to declare.

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