Transient hypoalgesia after COVID-19 infection

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Abstract

Introduction: Loss of smell or taste are often-cited complications during COVID-19 disease, but there is no clear evidence for affection of the peripheral nervous system.

Methods: Here, we report a 48-year-old man presenting with persistent dysgeusia and hypoalgesia of the lower legs, hands, and cheeks after COVID-19 infection in Spring 2020.

Results: Upon clinical examination 7 months after the infection, the patient could not feel pain after pinprick stimuli. Quantitative sensory testing revealed increased thermal detection thresholds at the face but no changes at the foot. Electrical C-fiber stimulation elicited lower pain ratings at the distal leg compared with the proximal leg, but overall higher pain ratings than in healthy control subjects. The axon flare reaction in response to histamine and acetylcholine was almost absent with no pain sensation. Skin punch biopsy revealed a reduced intraepidermal nerve fiber density at the lower leg, and transient receptor potential vanilloid 1 and calcitonin gene-related peptide immunoreactivity were similar to a healthy control. Symptoms and positive tests improved 5 months later.

Conclusion: In summary, we describe a case of hypoalgesia after COVID-19 disease. Studies investigating long-COVID syndrome should test not only for painful neuropathic symptoms but also for hypoalgesia, especially in patients with prolonged dysgeusia.

Keywords: SARS-CoV2, C fiber, Quantitative sensory testing, Axon flare

1. Introduction

Early signs of COVID-19 include olfactory and gustatory dysfunction.[8] This is sometimes accompanied by loss of capsaicin and menthol sensitivity (chemesthesis).[14] Most of the symptoms of COVID-19 disease are respiratory, but severe disease including multiple organ failure can develop. COVID-19 disease symptoms include pain, such as headache or myalgia and potentially neuropathic pain.[10,11] However, the affection of the peripheral nervous system is less clear: SARS-CoV2 enters cells in the body by binding to angiotensin-converting enzyme 2 (ACE2) receptor expressed on the cell surface.[11] Neuro-invasive behavior of SARS-CoV2 similar to MERS-CoV and HCoV-229E has been proposed,[8] specifically because ACE2 receptors are expressed on nociceptors.

Here, we describe a patient with parainfectious/postinfectious loss of taste/smell and transient reduced pain sensation after SARS-CoV2 infection and present full workup to assess C-fiber function.

2. Methods

The patient gave written consent to publish his case. C-fiber studies in patients and control persons were approved by the Ethics Committee of the University of Wuerzburg Medical Faculty (#272/19).

The patient presented at the pain clinic, was clinically examined, and answered self-administered questionnaires to assess the psychological well-being. Stress, depression, and anxiety were analyzed by the Depression, Anxiety and Stress scale. Workup included a routine blood analysis and nerve conduction studies and quantitative sensory testing (QST) following the standardized DFNS (German Research Network on Neuropathic Pain) protocol.[9] After QST in November 2020, skin punch biopsies were taken (5 mm; device by Stiefel GmbH, Offenbach, Germany) under local anesthesia from the left distal lateral calf 10 cm above the malleolus and the left proximal lateral thigh in February 2021. Specimens were processed for the assessment of skin innervation following standardized rules and as previously reported.[1,2] Additional stains included immunofluorescence for transient receptor potential vanilloid 1 (TRPV1) (ACC-

030 rabbit polyclonal antibody; Alomone Labs, Jerusalem, Israel) and CGRP (ab135271 rabbit polyclonal antibody; abcam, Cambridge, United Kingdom) with appropriate secondary antibodies.

To assess C-fiber function, we performed electrical and iontophoretic stimulation of the skin fibers in 2 regions in February 2021: at right distal lateral calf and right proximal lateral thigh. Driven from the symmetrical presentation of sensory deficits on our patient, we chose to perform these newly introduced tests on the body side that was predominantly examined in control subjects (right), to achieve mostly comparative with control subjects. Transcutaneous electrical C-fiber stimulation of the C fibers was performed with slowly depolarizing electrical pulses according to previously published protocols using 2 stimulation profiles, one with half-sine wave pulses and one with sinus wave pulses.[3,12] The electrical stimulus was delivered through L-shaped blunted bipolar platinum–iridium electrodes (diameter 0.4 mm, distance 2 mm; Cephalon, Nørresundby, Denmark), which were gently placed onto the skin. A constant current stimulator (Digitimer DS5; Digitimer Ltd, Welwyn Garden City, United Kingdom) and a pulse generator (NI USB-6221; National Instruments, Austin, TX) controlled by DAPSYS 8 (www.dapsys.net) generated (1) half-sine wave pulses of 500-ms duration (1 Hz) at current intensities of 0.2 to 1 mA ("half-sinus profile") and (2) sine wave pulses of 250-ms duration (4 Hz) at intensities of 0.05 to 0.4 mA for a 10-pulse and constant 1-minute sinusoidal stimulation ("sinus profile"). After this, we performed a noninvasive anodal dermal iontophoresis to deliver histamine (1% for 20 seconds at current intensity of 0.5 mA) and acetylcholine (10%, for 5 minutes at current intensity of 1 mA) into the upper skin layers following published protocols.[7,13] The patient's reported sensations at standard intervals according to protocol and during stimulation (pain, itch) and their intensities on an 11-point numerical scale (NRS; 0–10) were documented for both examinations. Results were compared with normative value obtained from 16 healthy volunteers (median age 55.5 years, range 23–76) in our laboratory. We also measured the area of the induced flare response at 15 minutes after iontophoresis.

3. Results

A 48-year-old male patient presented to the Interdisciplinary Pain Centre of the University Hospital Wuerzburg, Germany, in November 2020 with loss of pain sensation. This had first become fully apparent in September 2020, when he underwent surgery of his right knee and did not feel postsurgical pain or pain during physiotherapy. HbA1c, vitamin B$_{12}$, and folic acid revealed to be normal in the blood examination. No regional anesthetics had been used during the operation. The patient stated that he suffered from sensory loss not only on both legs but also on his hands. For example, he could only detect tissue damage by visual signs, such as bleeding. The patient had never noticed such symptoms before and denied other comorbidities or any regular medication.

However, his gustatory and olfactory senses were severely impaired since COVID-19 disease starting April 12, 2020, with mild flu-like symptoms. He was tested positive at the University Hospital Wuerzburg on April 17, 2021 (ct value 30.8). Throat swabs remained weakly positive until May 22, 2020 (ct value between 30.6 and 36.2). No medical treatment or hospitalization was necessary. Because of the persistence of positive real-time quantitative polymerase chain reaction (qPCR) results, specimens were further analyzed: on May 22, 2020, the Orf1ab qPCR of the throat swab was still positive, but the E protein qPCR was negative. No viable SARS-CoV-2 particles were detected using

Vero cell culture, and IgG antibodies against SARS-CoV-2 were found in the blood. So, the patient was released from quarantine. On May 29, 2020, the qPCR was negative.

In November 2020, the patient was treated for 10 days with prednisolone 5 mg/d by his otorhinolaryngologist to potentially suppress an immune reaction responsible for the loss of taste and smell. The patient did not report any improvement under this treatment.

The patient was overweight (body mass index of 36 kg/m^2). Onychomycosis could be detected on both feet, while the skin was otherwise normal. Motor function and gait were normal. Light touch was felt normally, but pinprick sensitivity was reduced, and the patient detected only a dull feeling in the lower legs and feet. Temperature sensation was also reduced at both lateral calves. The cranial nerves were intact. Hands and the umbilical region were not examined at the bedside.

A cranial magnetic resonance imaging performed in October 2020 because of persistent anosmia and ageusia did not reveal any intracranial pathology. Routine blood analysis was within laboratory ranges except for elevated lipids. Nerve conduction studies of the right tibial and sural nerves gave normal results, thus excluding a large-fiber neuropathy (**Figs. 1A–C**. No symptoms of anxiety, stress, or depression were detected in the Depression, Anxiety and Stress scale.

Quantitative sensory test performed in December 2020 at the right cheek and the dorsum of the right foot revealed increased cold detection thresholds in the face, but normal thresholds at the foot. The thermal sensory limen as well as cold and heat pain and all mechanical tests were normal (**Fig. 2**).

The intraepidermal fiber density was normal at the proximal thigh (10.7 fibers/mm, cut-off 8.5) and reduced at the distal leg (3.4 fibers/mm, cut-off 5.4) as compared with internal reference laboratory values. The subepidermal nerve plexus was diminished at both sites; sweat gland innervation was reduced at the lower leg. The patterns of peptidergic or TRPV1-immunoreactive axons were not different from a healthy control; in all of these, immunoreactivity was confined to few subepidermal nerve fibers (see supplemental figure 1, available at http://links.lww.com/PR9/A149).

C-fiber stimulation at a clinically affected area (pain loss at lower leg) using both the "sinus" and the "half-sinus" stimulation profile induced a mixed pain sensation (burning and stabbing). Pain intensity increased with current intensity as expected (**Figs. 3A and B**) but was lower at the distal leg than at the thigh after half-sinus stimulation in a within-patient comparison. Interestingly, pain ratings upon stimulation at the thigh were higher than in our group of healthy control subjects. The attenuation of pain intensity normally seen in healthy control subjects after a 1-min constant sinusoidal stimulation at lower leg did not occur in the patient (**Fig. 3C**).

Histamine and acetylcholine iontophoresis induced no pain sensation in the affected test area (lower leg) with very small flare area compared with the results of our group of healthy control subjects (**Figs. 4A and B**). Mechanical stimulation (von Frey filament 256 mN) in the test area after histamine iontophoresis induced no pain but itch sensation (2 points on NRS). No pain or itch sensation was observed after mechanical stimulation with lower intensity (von Frey filament 32 mN or cotton pad).

In the follow-up visit in May 2021—12 months after COVID-19 disease—the patient reported that he started to sense pain after intensive exercise (myalgia) and gustatory sensation returned for certain periods. On examination, he could now differentiate between cold and warm and correctly detected pinprick stimulation. Likewise, QST values had normalized except for an increased mechanical pain sensitivity at the foot and cheek
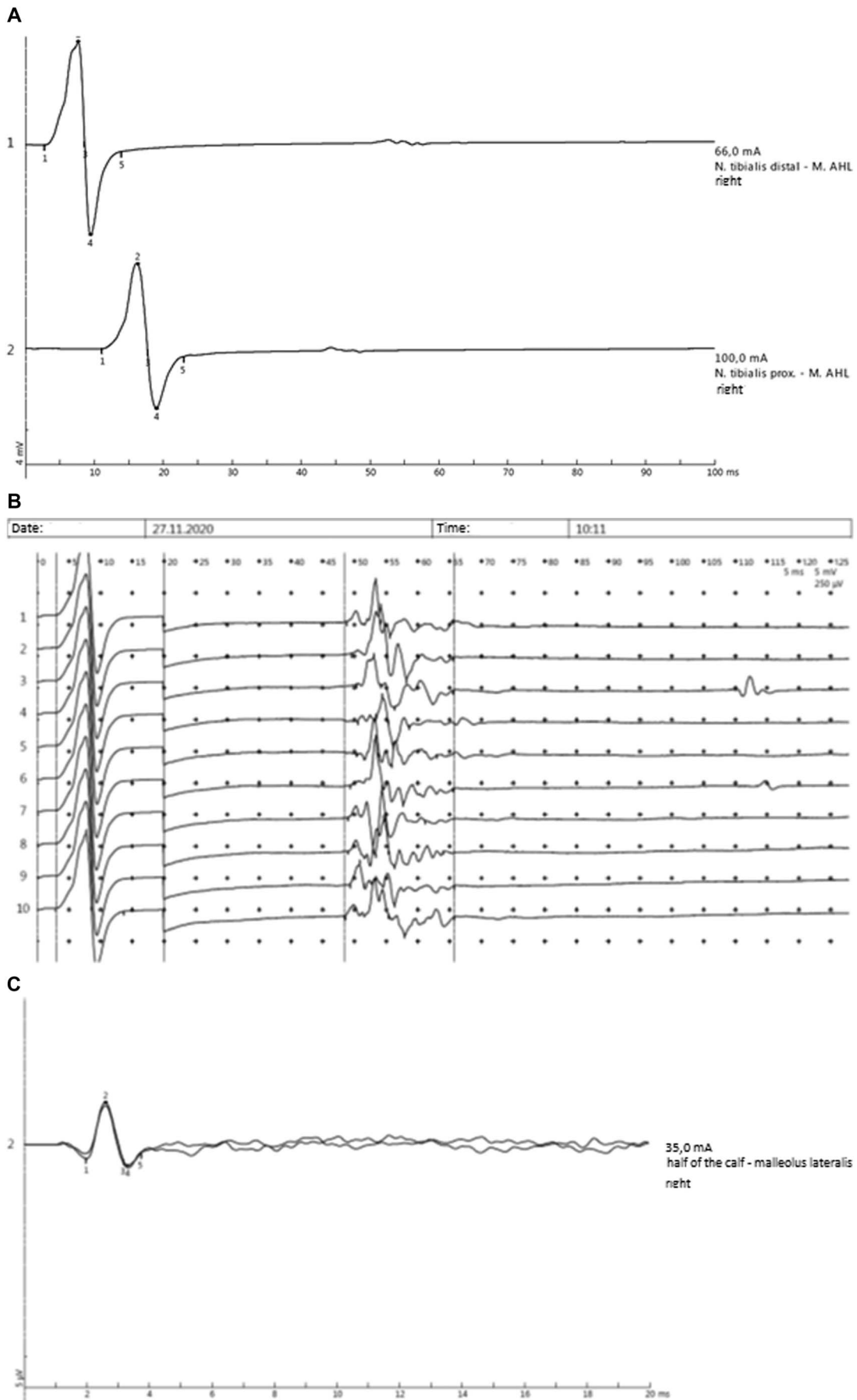
Figure 1. Normal nerve conduction studies (NCS) of the lower leg. (A) Motor NCS of the right tibial nerve; (B) F-wave of the right tibial nerve; (C) NCS of the right sural nerve (sensory, antidromic technique).
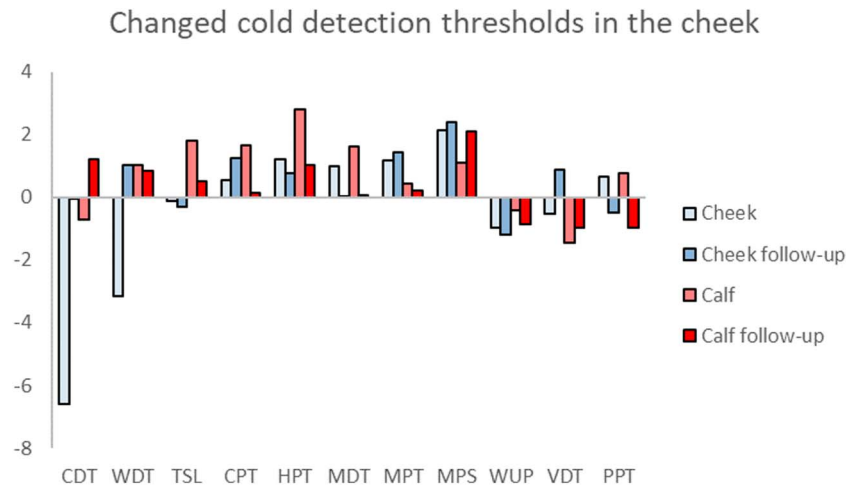
Changed cold detection thresholds in the cheek

Figure 2. Normalization of the quantitative sensory testing over time. Quantitative sensory test measurement at 2 sites at the time of presentation in December 2020 (calf and cheek, light red and light blue) and with gradual resolution of symptoms in May 2021 (calf and cheek follow-up, dark red and dark blue). CDT, cold detection threshold; CPT, cold pain threshold; DMA, dynamic mechanical allodynia; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, deep pain sensitivity to blunt pressure; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

(**Fig. 2**). C-fiber stimulation gave very similar results as before (**Fig. 3**). Iontophoresis-induced flare after histamine had normalized, but acetylcholine remained low (**Fig. 4**) revealing an improved function of histaminergic C fibers. Itch sensation after stimulation with a 256 mN von Frey filament remained unchanged (2 points on NRS).

4. Discussion

This study describes a patient with hypoalgesia and a loss of taste/smell after SARS-CoV2 infection that gradually improved 1 year after the COVID-19 disease. While loss of taste and smell are known features of COVID-19 disease, loss of pain sensation has not been documented in the literature. In-depth patient phenotyping revealed reduced skin innervation and histamine and acetylcholine reactivity. Electrical C-fiber stimulation evoked an altered response but not a complete loss.

The results of iontophoresis with histamine and acetylcholine provided evidence of low C-fiber reactivity at time of the first examination, which was normalized at follow-up. This leads to the conclusion that histaminergic and acetylcholine-reactive C fibers were initially affected and recovered later, in line with the clinical finding of hypoalgesia. The distal intraepidermal nerve fiber density was decreased, but no unusual pattern of TRPV1 or CGRP immunoreactivity could be seen (see supplemental figure 1 and 2, available at http://links.lww.com/PR9/A149). Thus, loss of sensory fibers might be responsible for hypoalgesia; however, intraepidermal nerve fiber density does not correlate well with function in neuropathy in general.[4]

Based on the clinical examination, we expected that electrical C-fiber stimulation of the distal leg would not elicit pain. The results of C-fiber stimulation using the "half-sinus" profile that activates polymodal nociceptors and the current intensity–dependent pain response[3,12] indicate the presence of excitable mechanosensitive nociceptors both at clinically affected and nonaffected areas of our
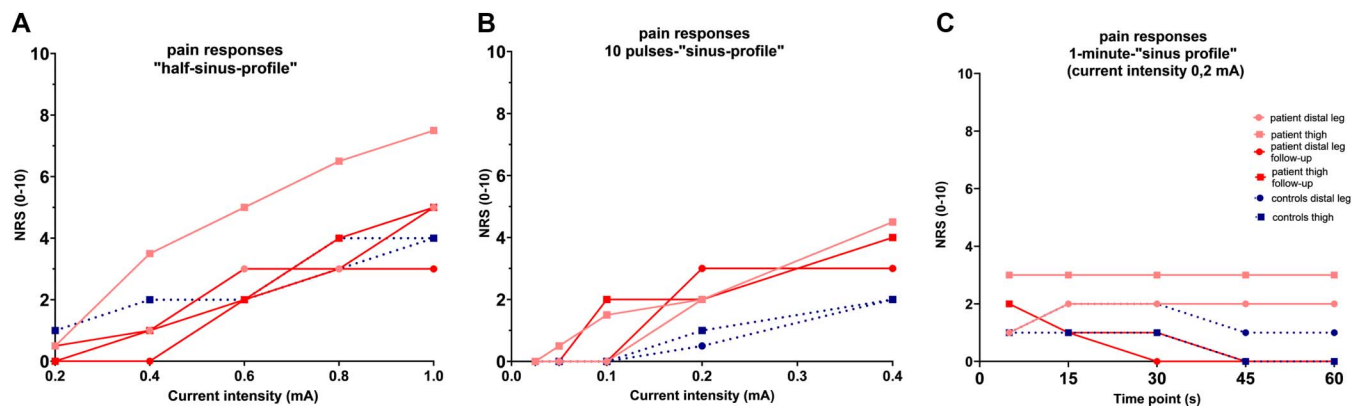

Figure 3. Altered C-fiber function in the patient with hypoalgesia and its resolution. (A) Induced pain response after stimulation with "half-sinus profile". A current intensity–dependent pain response was induced (light red), indicating an activation of mechanosensitive C-nociceptors, with a lower pain rating at the affected area compared with the proximal test area. (B) Induced pain response after stimulation with 10-pulses "sinus profile" showed a current intensity–dependent pain response, indicating an activation of mechanosensitive and silent C-nociceptors. (C) Induced pain response after stimulation with 1-minute "sinus profile." Differently to control subjects, no accommodation of induced pain intensity was observed in our patient (dotted blue lines indicate median induced pain report from a group of healthy control subjects, n = 46, median age 53.50 years). Test repetition after 3 months revealed no noticeable change of pattern (dark red). Affected area (circle), unaffected area (square).
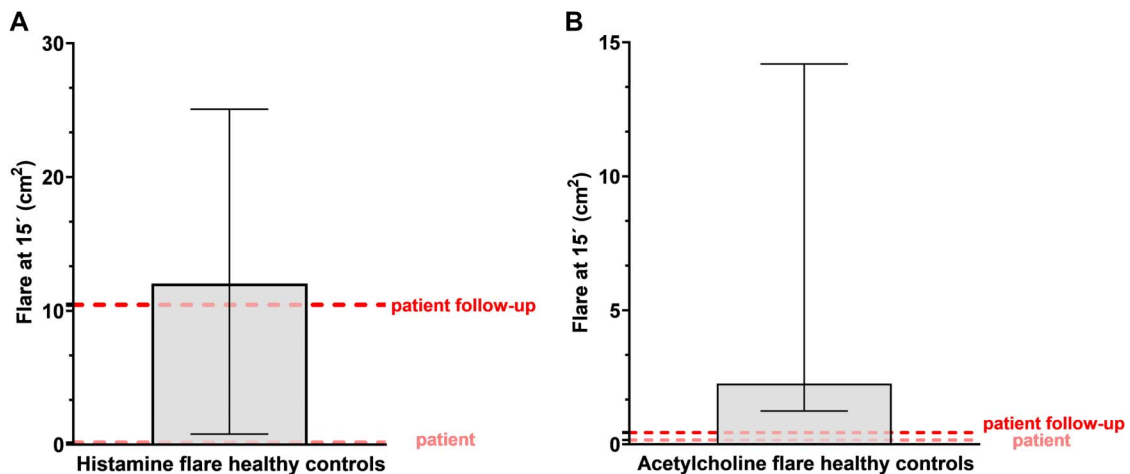
Figure 4. Reduced flare after iontophoresis with histamine (A) and acetylcholine (B) in the patient with hypoalgesia and its resolution. Shown are data from 16 healthy control subjects with median and range (median age 55.50 years). Dotted lines indicate value of the patient at the first presentation (light red) and at the follow-up (dark red).

patient, although slightly diminished at the affected area (lower induced pain intensity at lower leg). However, in general, induced pain intensity was higher compared with the reports of our group of healthy control subjects. The constant 1-minute sinusoidal stimulation at supra-threshold current intensities (0.2 mA) that activates both polymodal and silent nociceptors should induce an accommodation of C fibers[3] and thus reduce pain intensity over time. This was not present in the patient. This leads to the hypothesis that the induced pain sensation via C fibers (both silent and polymodal nociceptors) is unchanged, but that spontaneous activity or axonal hyperexcitability is present. Micro-neurography, although a time-consuming, invasive, and not widely available test, would be necessary to test these assumptions. In quantitative sensory testing, we expected to see a loss in response to painful stimuli, but there were only minor changes at the site of the clinical symptoms that normalized after 5 months. Thus, in addition to history and clinical examination, skin biopsy and measurement of axon flares were most helpful to identify the functional deficit.

Neurotropism is a known feature for SARS-CoV2 infection[8,10]: patients often complain of quantitative but also qualitative olfactory and taste impairment.[8] These symptoms are mainly transient for up to 21 days.[8] Our patient also complained about these symptoms at the time of presentation over 6 months after COVID-19 disease. Suffering from olfactory and taste impairment seems to be closely related to chronic pain.[15] Our patient showed a similar loss of function in the periphery as he specified not to feel any pain—just a dull feeling. We suggest that inpatients with prolonged ageusia or dysgeusia clinicians should look for signs of hypoalgesia.

The underlying mechanisms of dysgeusia are still being discussed including several peripheral and central hypotheses.[5,8,10] As neuro-invasive behavior has been verified for other viral infections such as MERS-CoV, it seems possible that SARS-CoV2 is also character-ized by this feature.[8,16] Changes in sensation after SARS-CoV2 infection may be linked to the ability of the virus to bind to ACE2 receptors present on human dorsal root ganglion.[6,11,14] Similarly, the 2 main proteases for the SARS-CoV2 spike protein priming, TMPRSS2 and FURIN, are also found in human and mouse DRGs. One could postulate that the virus enters sensory neurons via ACE2 receptors and harms the axons as seen in the skin punch biopsy with decrease of intraepidermal nerve fibers and the loss of the histaminergic response. Alternatively, the interaction of NRP-1, VEGF-A, and SARS-CoV2 may be responsible for part of the presented symptoms[11]: blocking the binding site of VEGF-A to NRP-1, as described for SARS-CoV2 spike protein, could ameliorate or prevent proper pain sensation in affected patients.[11]

Obviously, we cannot completely rule out other reasons for the observed hypoalgesia, abnormal QST, and reduced intraepider-mal fiber density. Because the patient is obese and received a steroid pulse, a small fiber neuropathy is possible. However, his symptoms were present before this short, low-dose steroid treatment was administered, and HbA1c as well as a routine workup for neuropathy were normal.

In summary, we report a peculiar patient with a transient reported hypoalgesia as a complication caused by COVID-19 disease. Long-term population studies should include these symptoms and the outlined tests into their portfolio to understand the relevance of the clinical finding as well as studying this in preclinical models in more detail.

Disclosures

Acknowledgements

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A149.

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