

Case Report

Cutaneous hyperalgesia in the setting of COVID-19 infection: reporting 2 cases from North India

Ipshita Bhattacharya^{1*}, Ananta Kanwar², Keshav Sachdeva³, Vishnu Choudhary⁴

¹Department of Dermatology, Venereology and Leprosy, ESI-PGIMS Hospital, New Delhi, India

²Department of Obstetrics and Gynaecology, VMMC and Safdarjung Hospital, New Delhi, India

³Department of Cardiology, Batra Hospital and Medical Research Centre, New Delhi, India

⁴Department Of Dermatology, Venereology and Leprosy, Brijesh Banger Hospital, Bhilwara, Rajasthan, India

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*Correspondence:

Dr. Ipshita Bhattacharya,

E-mail: ipshita95in@gmail.com

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ABSTRACT

COVID-19 (Coronavirus disease) infection can manifest with a variety of dermatological and neurological symptoms which might have similar underlying patho-mechanisms. Here we report 2 cases of rt-PCR (Real time PCR) positive COVID infection who developed cutaneous hyperalgesia during the illness and review the case reports, case series, and other literature available on this symptom. We found that out of the total 13 reported cases (including the two cases reported here), most common onset of this symptom was within the first 3 days of illness (median duration ten days). Common sites of involvement included abdomen and back, but chest, arms and legs could also be involved. Warm baths, gabapentin and pregabalin showed good efficacy in relieving the symptom. The exact pathogenesis remains unclear but is hypothesised to be due to the neurotrophic properties of the virus and/or the inflammatory cytokines released during the illness. Further studies are necessary to expand the scope of knowledge in this regard.

Keywords: COVID-19, COVID infection, Cutaneous hyperalgesia

INTRODUCTION

Amid the massive second wave of COVID-19 infection raging through India, a plethora of newly reported COVID associated symptoms have emerged. One such symptom is cutaneous hyperalgesia, which refers to increased sensitivity of skin. There is paucity of literature regarding this particular symptom, of which only 11 other cases have been reported till date.¹⁻³ We aim to compare and analyse the available case reports to better understand the neuropathic nature of the causative SARS CoV-2 and further discuss its implications.

CASE REPORT

Here we report 2 cases who developed cutaneous hyperalgesia during the course of an rt-PCR confirmed COVID-19 infection.

The first patient, a 29-year-old female, reported increased sensitivity to touch 17 days after onset of symptoms (fever, weakness, and dry cough). It was first experienced while changing of clothes and gradually increased in intensity even with the slightest touch. Areas of distribution included abdomen, chest, back and arms, and were not restricted to a specific dermatome. No other skin changes were present. It was relieved with Pregabalin. Initially she required Pregabalin 75 mg twice daily for 2 days followed by once daily for 2 days after which she stopped medication as she was able to tolerate the pain, but the pain persisted for 9 days. Other medications taken included Tablet Methylprednisolone 10 mg OD for 5 days, Tablet Rivaroxaban 15 mg OD for the 1 week, and a multivitamin tablet for 1 week containing vitamin B12 1000 ug, folic acid 1.5 mg, pyridoxine 3 mg, inositol 100 mg, benfotiamine 100 mg, and alpha lipoic acid 200 mg.

The second patient, a 25-year-old male, reported increased sensitivity to touch on the same day of onset of general symptoms (fever and weakness). Heightened sensitivity was present predominantly over the back. It was tolerable to the patient and got relieved after 15 days of onset without any medication. No other skin changes were present. Other medications taken for COVID infection are not known.

DISCUSSION

Data from all available case reports were tabulated and analysed as shown in the Table 1. Most patients were in younger age group (25-44 years), mean age 44 years (n=11). 46% (6 out of 13) were male and 53% (7 out of 13) were female, with almost equal male to female ratio. Most developed hyperalgesia within first few days of onset of general symptoms (mean 5.2 days, median=Same day of onset of general symptoms, n=9), while 1 patient each reported it 2 days before and 5 days after resolution of symptoms. The median duration was 10 days (mean 27.9 days, n=10), Notably in 1 case hyperalgesia persisted for 6 months. Most common sites affected were back (83.34%, 5 out of 6 patients) and abdomen (66.67%, 4 out of 6 patients). Warm baths, Gabapentin and Pregabalin provided relief in these patients as shown in the Table 1.

Cutaneous symptoms of COVID-19 broadly include pseudo-chilblains (pernio-like), vesicular rash, maculopapular exanthem, urticaria, and livedo reticularis, but certain rarer symptoms have emerged. These entail reactivation of herpes simplex/herpes zoster, erythema-multiforme like lesions and cutaneous hyperesthesia.⁴

As of this date, 13 cases of COVID-19 associated cutaneous hyperalgesia have been reported in English literature, including the 2 cases reported here.¹⁻³ To the best of our knowledge, this is the first such report from India.

Our findings are coherent with previous reports and within range in terms of demographic profile of these patients, time of onset, distribution, and duration of symptoms. However, whether hyperalgesia is more common in a certain severity of COVID or more common in association with particular symptoms (like fever, cough, anosmia) cannot be commented on due to insufficient data and inability to reasonably apply statistics analysis on such a small sample size.

One notable observation is that 2 patients developed an itchy, papular, scaly, exanthem during their illness, of which 1 patient reported that the hyperalgesia spared the areas affected by the rash.^{1,5} Since the rash was an itchy, scaly, exanthem it was likely a maculopapular drug eruption possibly triggered by medications the patient might have taken for COVID illness.

The intensive cross-communication between skin and the nervous system is well known. In setting of viral infections, this is highlighted especially in the case of Herpes Zoster (HZ). HZ occurs due to reactivation of latent Varicella Zoster Virus (VZV) in the dorsal root ganglion of cranial or spinal nerves. It occurs as an erythematous rash followed by vesicles/ pustules which crust and scab. It is typically unilateral and dermatomal in distribution and maybe associated with burning/tingling pain, allodynia (pain provoked by non-painful stimulus such as light touch) and hyperalgesia (Exaggerated response to painful stimulus).⁶ Neural symptoms are attributed to inflammation of peripheral nerves with resultant demyelination, Wallerian degeneration, and fibrosis, thus increasing activity in unmyelinated primary afferents.⁷

Similarly, COVID-19 associated neurological symptoms can be attributed to (1) direct neurotropic nature of SARS-CoV2 (similar to VZV) and/ or, (2) Secondary to nerve injury due to the pro-inflammatory cytokines.

Viruses of *β-coronaviridae* family are known to be neurotropic for central as well as peripheral nervous system. Both SARS-CoV2 and SARS have been demonstrated within brain tissue, notably the brainstem. It is hypothesised that SARS-CoV2 enters cerebral circulation via endothelial cells which express ACE2 receptors. While brain and peripheral nerves have low expression of ACE2 receptors, it is hypothesised that they have an unknown receptor for the spike protein of *β-coronaviruses* which accounts for its affinity for these tissues.⁸⁻¹⁰

Pro-inflammatory cytokines (especially in the setting of cytokine storm) could also be responsible for neural symptoms. However, hyperalgesia has also been reported in a patient with normal levels of CRP, IL-6, D-Dimer, Fibrinogen, LDH and creatine kinase.³ Thus, more studies are required to conclusively comment on this.

CONCLUSION

Thus, Cutaneous hyperalgesia is emerging as a novel symptom of COVID-19 infection. While it may be partially attributed to neurotropism of the virus, the exact etiopathogenesis remains to be understood. Further studies are required to probe whether this symptom denotes a particular severity of the disease in terms of symptoms or biochemical markers, and whether it can be associated with other neurological symptoms (such as anosmia etc). Clinically, cutaneous hyperalgesia needs to be differentiated from the Herpes Zoster. Medication targeting neuropathic pain like Pregabalin and Gabapentin is considered to be effective. Supportive management can be done in the form of warm baths. Role of the vitamins (like vitamin B-12) supplementation needs to be explored.

Table 1: Patient characteristics.

Reported by	Age (Years)	Sex	Symptoms	Distribution	Onset (Within days of general symptoms)	Duration (Days)	Relieving factors	Treatment taken (Apart from that for cutaneous hyperalgesia)	Additional skin findings
Krajewski¹	40	M	Fever, malaise	Whole body (Predominantly abdomen and back)	Same day	10	Warm bath	HCQS*	No
	40	F	Fever, dry cough, pneumonia, dysgeusia	Whole body (Predominantly abdomen and back) notably spared the areas affected by rash on day 5.	Same day	10	Diclofenac	HCQS	Itchy scaly exanthem
	44	M	Asymptomatic	No data	5 days after resolution	6 M	None	Gabapentin, Duloxetine	No
	No data	F	No data	No data	14 th day	No data	No data	Inj. Diclofenac, Inj. Vit B	No data
	62	F	Fever, myalgia, fatigue	No data	2 days before	1	Aspirin	Aspirin	No
	29	M	Fever, dry cough and fatigue	No data	4 th day	6	No data	No data	No
	49	M	Burning sensation in nose and anosmia	No data	No data	No data	No data	No data	No
	57	F	Fever, fatigue	No data	3 rd day	10	Warm bath	Metamizole	Itchy scaly exanthem
	42	M	Fever, fatigue, headache	No data	3 rd day	No data	#NSAIDs	^{\$} PCM, Aspirin	No
Harsch²	68	F	No data	Abdomen and legs	Day of admission	8	No data	No data	No
Aksan³	40	F	Fever, body ache, cough, anosmia, ageusia	Neck and back	6 th day	>1 M	Gabapentin	HCQS, Apixaban, oral prednisone, nebulised Albuterol and Ipratropium	No
Bhattacharya	29	F	Fever, fatigue, dry cough	Abdomen, chest back and arms	17 th day	9	Pregabalin	[^] MPS, Rivaroxaban, ⁺ MVT	No
	25	M	Fever, fatigue	Back	Same day	15	Not needed	No data	No

*HCQs-Hydroxychloroquine, #NSAIDs-Non steroidal anti-inflammatory drugs, ^{\$}PCM-Paracetamol, [^]MPS-Methyl prednisone, ⁺MVT-Multivitamin)

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