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

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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.

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

Received: 15 May 2021
Revised: 08 June 2021
Accepted: 09 June 2021

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

*HCQs-Hydroxychloroquine, #NSAIDs-Non steroidal anti-inflammatory drugs, $PCM-Paracetamol, ^MPS-Methyl prednisone, +MVT-Multivitamin*
Funding: No funding sources  
Conflict of interest: None declared  
Ethical approval: Not required

REFERENCES
