



Original Research

Neuropathic Pain in Hospitalized Patients With COVID-19: A Prospective Case Series



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KEYWORDS

COVID-19;
Neuralgia;
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Abstract Objective: To report the demographic and clinical characteristics of 8 patients hospitalized with COVID-19 and presenting with neuropathic pain (NeuP).

Design: A prospective case series with 1-month follow-up.

Settings: COVID-19–dedicated wards of a tertiary care center.

Participants: We included 8 consecutive cases of laboratory-confirmed cases of COVID-19 (by reverse transcription polymerase chain reaction) who presented with NeuP during the course of their acute hospitalization (N=8).

Interventions: Not applicable.

Main Outcome Measures: A verbal rating scale was used to assess NeuP severity at presentation and at 1-month follow-up. The Douleur Neuropathique 4 questionnaire was used to diagnose NeuP at presentation.

Results: Most patients were diagnosed as moderate to severe COVID-19 (6/8) and presented with mild to moderate NeuP (6/8). A substantial proportion of patients (4/8) displayed persistence of mild pain symptoms at 1-month follow-up. Furthermore, participants displayed a favorable response to gabapentinoids with or without antidepressants.

Conclusion: NeuP is a less commonly encountered symptom of COVID-19, but its early diagnosis and prompt management are of utmost importance. More studies including a larger cohort and longer follow-up are recommended for better understanding of COVID-19-associated NeuP.

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List of abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; DN4, Douleur Neuropathique 4; NeuP, neuropathic pain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VRS, verbal rating scale.

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COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared as a worldwide pandemic by World Health Organization on March 11, 2020.¹ The clinical characteristics of COVID-19 are still evolving and are the subject of extensive research. Besides the common respiratory manifestations of COVID-19, it has been shown to involve almost any system in the human body. Neurological manifestations are not uncommon and may involve both central and peripheral nervous system involvement. Common neurologic symptoms of COVID-19 are anosmia, ageusia, and headache. There are also reports of myelitis, stroke, and Guillain-Barré syndrome.² Furthermore, it is well established that pain symptoms are among the most common clinical manifestations of the disease. Myalgia and headache are among the most commonly reported pain symptoms.³⁻⁵ COVID-19-associated neuropathic pain (NeuP) has been investigated in less detail so far, with scarce reports in the literature. A recent study reported possible neuropathic pain in up to 2.3% of hospitalized patients with COVID-19.⁶ Therefore, we aim to report 8 consecutive cases of COVID-19-associated NeuP and their detailed clinical and demographic characteristics.

Case presentation

A confirmed case was defined as a person with laboratory confirmation of COVID-19 infection (by reverse transcription polymerase chain reaction), irrespective of clinical signs and symptoms. Severity classification was done according to the guidelines issued by the Ministry of Health and Family Welfare, Government of India.⁷ A verbal rating scale (VRS; 0-10) was used for the severity assessment of NeuP and the Douleur Neuropathique 4 (DN4) questionnaire was used for the diagnosis of NeuP. Pain severity classification was done as mild (VRS 1-3), moderate (VRS 4-7), and severe (VRS 7-10). A minimum score of 4 (out of 10) on the DN4 questionnaire was considered as NeuP. All patients were followed up at 1 month for the persistence of symptoms. Written informed consent was signed by all participants before inclusion in the study.

Case 1

A 66-year-old male patient was diagnosed with moderate COVID-19 and was on corticosteroids and remdesivir injections along with other supportive treatments. He had a body mass index (BMI) of 24.9 kg/m² with no significant past medical history. On the fourth day of his illness, he developed new-onset pain described as pins and needles sensations involving the lateral aspect of both his legs and feet. The pain symptoms were in the distribution of common peroneal nerve bilaterally. No objective signs could be elicited on clinical examination. Pain severity on VRS was 5 and was exaggerated with prolonged bed rest and relieved with standing or walking a few steps. The pain was persistent during the night and was interfering with his sleep (DN4 score of 4). He was prescribed 75-mg tablets of pregabalin with 10 mg of amitriptyline at bedtime and advised to avoid prolonged bed rest. Pain improved significantly over the next 3-

4 days, and the VRS score at discharge was 2. At 1-month follow-up, the pain had subsided completely (VRS score of 0).

Case 2

A 40-year-old male patient with a BMI of 26.0 kg/m² and no significant past medical history was diagnosed with mild COVID-19. He was only on supportive medications without the need for oxygen support. The patient gave a history of addiction to alcohol. On the seventh day of his illness, he complained of current-like sensations over his left lower limb in the sciatic nerve distribution that caused sleep impairment. The pain was aggravated when lying prone for a prolonged period (to improve oxygenation) and was improved with other postures. Pain severity was rated 5 on VRS with a DN4 score of 4. He was prescribed 75-mg tablets of pregabalin with 10 mg of amitriptyline at bedtime with an intermittent change of postures. Due to an inadequate response, the dose of pregabalin was increased to 150 mg (75 mg twice daily). At discharge, the pain improved to a VRS score of 3 with improvement in sleep. At 1-month follow-up, there was a significant improvement in pain (VRS score of 1).

Case 3

A 24-year-old male patient on supportive treatment was diagnosed with mild COVID-19. He had no history of any significant medical illness but was a chronic smoker. On the fifth day of his illness, he developed pins and needles sensations over both of his upper and lower limbs. The pain severity was rated as 3 on VRS with a DN4 score of 5. There was no correlation of pain with postural change or activities. The symptom improved without any treatment over the next 2-3 days. At 1-month follow-up the patient reported no pain (VRS score of 0).

Case 4

A 52-year-old male patient was diagnosed with severe COVID-19 and was on ceftriaxone, dexamethasone, and remdesivir, along with supportive medications. He had a BMI of 27.1 kg/m² with a known history of type 2 diabetes mellitus. On the eighth day of his illness, he developed new-onset pins and needles sensation in both of his hands along with the median nerve distribution, similar to that of carpal tunnel syndrome. There was an associated feeling of numbness, and hypoesthesia to touch was demonstrated on examination. He rated his pain intensity as 6 on VRS and the DN4 score was 5. The patient also reported sleep impairment attributable to the pain symptoms. He was prescribed 75-mg tablets of pregabalin that was titrated up to 150 mg/day, along with 10 mg of amitriptyline and 1500 µg/day of methylcobalamin. At discharge, the VRS score was 4 with improvement in numbness. At the end of 1 month, the VRS score was 2/5 with reduced frequency of symptoms and improved sleep.

Case 5

A 62-year-old male patient with a history of hypertension and chronic kidney disease was diagnosed with severe COVID-19. His BMI was 21.3 kg/m². On the 11th day of his illness, he presented with burning sensations over his lower back and both lower limbs, with a severity rating of 7 on VRS. The pain was aggravated with prolonged bed rest and improved with standing and walking a few steps. The pain was associated with hypesthesia to touch and the DN4 score was 4. He was started with 75-mg tablets of pregabalin along with 1500 µg/day of methylcobalamin. His pain improved over the next 2 weeks, and at 1-month follow-up there was significant relief in pain symptoms (VRS score of 2 out of 10).

Case 6

A 68-year-old male patient with no significant past medical history was diagnosed with severe COVID-19. He was a chronic smoker with a BMI of 22.1 kg/m². He was on remdesivir, corticosteroids, antibiotics, and other supportive treatment. On day 10 of his illness, he experienced a burning sensation over his whole body that was rated 5 on VRS. The DN4 score was 4 out of 10. The pain was constant and there was no relation to posture or any other factors. The pain settled down in the next 4-5 days with daily pregabalin (75 mg) without any additional treatment. At 1-month follow-up the patient did not report any similar symptoms and the VRS score was 0.

Case 7

A 51-year-old female patient with no history of any chronic illness was diagnosed with moderate COVID-19. Her BMI was 23.3 kg/m² with no addiction history. She was on corticosteroids and other supportive medications. On day 7 of her illness, she complained of an intense burning sensation over her chest and upper back in a dermatomal pattern from the T4-T8 region, and the pain severity was rated as 9 on VRS. There was associated numbness with hypesthesia to touch and prick. The DN4 score was 5 out of 10. She was prescribed pregabalin tablets titrated up to 150 mg/day along with 10 mg/day of amitriptyline. Her pain severity improved, with a VRS score of 4 at discharge. At 1-month follow-up

pain, severity was rated 3 on VRS and was reduced both in frequency and intensity.

Case 8

A 34-year-old male patient with no history of medical illness was diagnosed with moderate COVID-19. He had a BMI of 26.3 kg/m² with no history of addiction. He was on minimal oxygen support, dexamethasone, and remdesivir, along with other supportive medications. On day 5 of his illness, he presented with pins and needles sensation over both of his lower limbs associated with painful cold sensation. Examination was notable for mild weakness in knee flexion and ankle dorsiflexion. The pain severity was rated 6 on VRS and the DN4 score was 6 out of 10. He was prescribed 75-mg/day tablets of pregabalin and 10 mg of amitriptyline. The pain severity on VRS improved to 4 at discharge. At 1-month follow-up, the VRS score was 0 with complete resolution of symptoms.

Discussion

In this study, NeuP was seen predominantly in the male population (7/8) and moderate to severe COVID-19 (6/8). The latter finding supports the fact that neurologic symptoms are more common in severe COVID-19. The pain severity was predominantly mild to moderate (6/8) with a VRS score of 1-6. Severe NeuP (VRS \geq 7) was present in only 2 patients. All patients responded to gabapentinoids with or without antidepressants, supporting the neuropathic etiology of the pain symptoms. But it remains unclear whether the improvement in NeuP was due to the anti-neuropathic pain medications, corticosteroids, or a synergistic effect of both. One important finding that needs special attention is the persistence of mild NeuP symptoms in 50% of patients at 1-month follow-up. In a study evaluating persistent neuropathic pain in patients with COVID-19, moderate to severe COVID-19, azithromycin intake, and depression were identified as the associated factors.⁸ The detailed demographic and pain characteristics of 8 patients in this study are summarized in [Tables 1 and 2](#).

There are very few reports of incidence of NeuP among patients with COVID-19 associated with or without other neurologic complications. Aksan et al reported 1 case of a

Table 1 Demographic and baseline characteristics of 8 participants

Baseline Characteristics	Case							
	1	2	3	4	5	6	7	8
Age (years)	66	40	24	52	62	68	51	34
Sex	Male	Male	Male	Male	Male	Male	Female	Male
BMI (kg/m ²)	24.9	26.0	24.7	27.1	21.3	22.0	22.9	26.3
COVID-19 Severity	Moderate	Mild	Mild	Severe	Severe	Severe	Moderate	Moderate
Comorbidities	None	None	None	T2DM	HTN, CKD	None	None	None
Addiction	None	Alcohol	Smoking	None	None	Alcohol, smoking	None	None
Corticosteroid treatment	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Oxygen support	Yes	No	No	Yes	Yes	Yes	Yes	Yes

Abbreviations: T2DM, type 2 diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease.

Table 2 Clinical characteristics of neuropathic pain among 8 participants.

Case	Day of Onset	Character	Site	VRS Score	DN4 Score	Treatment	VRS (at 1 Month)
1	4	Pins and needles	Bilateral LL	5	4	Pregabalin 75 mg Amitriptyline 10 mg	0
2	7	Tingling	Left LL	5	4	Pregabalin 150 mg Amitriptyline 10 mg	1
3	5	Pins and needles	Bilateral UL and LL	3	5	None	0
4	8	Electric shocks	Bilateral hand	6	5	Pregabalin 150 mg Amitriptyline 10 mg	2
5	11	Burning	Back and Bilateral LL	7	4	Pregabalin 75 mg	2
6	7	Burning	Whole Body	3	4	Pregabalin 75 mg	0
7	10	Tingling	Chest and upper back	9	5	Pregabalin 150 mg Amitriptyline 10 mg	3
8	5	Painful cold	Bilateral LL	6	6	Pregabalin 75 mg Amitriptyline 10 mg	0

Abbreviations: LL, lower limb; UL, upper limb.

female in her 40s who presented with intense burning pain during her COVID-19 illness.⁹ The pain involved the neck and back from C1 to the L4-L5 region, with an intensity rating of 7/10. Siepmann et al described a case of a 52-year-old man with neuralgic amyotrophy after SARS-CoV-2.¹⁰ Another case of pure sensory neuralgic amyotrophy causing excruciating pain in the upper limb was reported by Cacciavillani et al.¹¹ In a more recent report, a 61-year-old man developed intense burning pain involving the whole body 1 week after testing positive for SARS-CoV-2.¹² More recently, Berra et al reported a series of cases of COVID-19 presenting with focal peripheral neuropathies.¹³ Common peroneal neuropathy, sciatic neuropathy, ulnar neuropathy, brachial plexopathy, and lumbosacral plexopathy are the commonly diagnosed conditions reported so far.^{13,14}

Pain symptoms are the well-known clinical manifestation of SARS-CoV-2, but less is known about the incidence and characteristics of neuropathic pain caused by the virus. SARS-CoV-2 is known to cause neurologic symptoms either by direct invasion of the nervous system or by virus-associated immune reactions.^{15,16} In the past, several viral infections have been reported to cause neurologic complications, including Epstein-Barr virus, coronaviruses, hepatitis virus, human immunodeficiency virus, cytomegalovirus, hepatitis virus, Zika virus, and influenza A virus.¹⁷ The neurologic complications include Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy in particular. Furthermore, SARS-CoV-2 has been recently shown to cause neurologic complications including stroke, myelitis, Guillain-Barré syndrome, and encephalitis.² All of these neurologic complications have the potential to cause NeuP. Cytokine storms can act as an important trigger for the development of neuropathies. In addition to direct virus-mediated effects, several other factors might be considered as triggers for NeuP. Prolonged prone positioning to improve oxygenation may lead to pain because of direct pressure effects on superficial peripheral nerves. Also, NeuP might occur as an adverse effect of medications used in these patients.

Study strengths and limitations

The strength of our study includes the prospective assessment of the NeuP symptoms for a period of 1 month indicating persistence of mild symptoms in a significant proportion of patients. In addition, this study furthers the debate on the response of COVID-19-associated NeuP to the conventional anti-neuropathic pain medications. There are certain important limitations of our study that need mention. First, a very small sample size prevents the generalizability of the findings. Second, we could not objectively assess the cause of the neuropathic pain because of the COVID-19 regulations and to avoid cross-infection. Third, a longer follow-up could have provided a better understanding of the persistence of NeuP. Nevertheless, this study opens the door to further research focusing on NeuP characteristics in a wider population, including their objective assessment. Furthermore, this study will guide health care workers in the early detection of such symptoms and their prompt management, which may prevent the development of chronic pain.

Conclusions

Neuropathic pain is a less frequent yet recognized manifestation of COVID-19. Considering the burden of COVID-19, we anticipate that many patients infected with SARS-CoV-2 will develop NeuP during the acute stage of the disease. COVID-19-associated NeuP is mostly mild to moderate in severity and responds well to anti-neuropathic pain medications. Therefore, early diagnosis and proper management are of importance to prevent its persistence. If left untreated, the pain symptoms can persist in a substantial proportion of patients and prolong recovery, thereby affecting quality of life. Further prospective evaluation is needed to delineate the prevalence, clinical characteristics, and persistence of NeuP among patients with COVID-19.

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