Possible complex regional pain syndrome following SARS-CoV-2 infection: Case report

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Abstract
SARS-CoV-2 infection has various manifestations including neurological and musculoskeletal system involvement. COVID-19 infection causes peripheral nerve lesions including small fibre neuropathy. Complex regional pain syndrome is a debilitating neurological condition manifested by predominantly pain associated with other sensory, motor, autonomic and tropic involvement. Identification and early treatment of CRPS has better prognosis. Here, we report a 21-year-old woman presented with pain, hyperalgesia, and swelling of left upper and lower limb following SARS-CoV-2 infection managed as possible complex regional pain syndrome.

Keywords
Complex regional pain syndrome, SARS-CoV-2, COVID-19, coronavirus, pain

Date received: 29 December 2021; accepted: 22 March 2022

Introduction
Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has widespread of clinical manifestation from asymptomatic, mild upper respiratory symptoms to fatal multiorgan failure and death. Although most patients develop pulmonary manifestations, several extrapulmonary manifestations have been associated including the nervous system and musculoskeletal system. Common manifestations of nervous system involvement include headache, anosmia and stroke. But rare serious manifestations like Guillain–Barré syndrome, encephalitis, myelitis, necrotizing hemorrhagic encephalopathy and focal status epilepticus have been reported.¹⁻³ Painful neuropathy, plexopathy and radiculopathy have been also reported following COVID-19 infection.⁴ Studies have also described musculoskeletal dysfunction in COVID-19 infection.⁵

We present a case of severe pain, hyperalgesia, and swelling of left upper and lower limb in a previously healthy person following mild SARS-CoV-2 infection managed as possible complex regional pain syndrome (CRPS).

Case report
A 21-year-old healthy woman with no significant past medical history developed upper respiratory tract symptoms and found to be positive for SARS-CoV-2 infection and monitored at a COVID-19 isolation centre. She had only a mild disease and managed with symptomatic treatment and was discharged home on day 10. On 14th day of illness, she developed generalized hyperalgesia which was particularly involving left 4th and 5th finger. This subsequently progressed with increasing pain from left side of the neck radiating up to left upper limb over 1 week and involved her left lower limb as well. In addition, she reported a mild swelling of left upper and lower limb (Figure 1(a) and (b)) and hyperalgesia. Symptoms have worsened over the next 4–5 days and made her totally difficult to move her limbs and neck. She denied any cramps, discoloration or any rash and reported no weakness, numbness, unsteadiness, swallowing difficulty, breathing difficulty or any dysarthria. There were no postural dizziness, dry mouth, dry eyes, bowel or bladder dysfunction. She was a teetotaler and denied any recreational drug use. Her neurological examination apart from hyperalgesia and allodynia was unremarkable. Power could not be

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assessed due to significant pain and reflexes are within normal limits with negative Babinski’s sign.

Initial investigations revealed done on day 4 of illness leucocytosis (white blood count (WBC) – 22,000) with mildly elevated erythrocyte sedimentation rate (ESR – 42 mm/1st hour) which subsequently reduced to normal. C-reactive protein was normal (<5). Serum creatinine was 0.7 mg/dL and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 32.5 and 47.6 U/L, respectively. Antinuclear antibody (ANA) and rheumatoid factor (less than 20 U/mL) were normal. Mildly elevated creatinine phosphokinase of 311 U/L (50–250) was noted and subsequently became normal. 25-hydroxy vitamin D level was found to be low (11 ng/mL) was corrected with 300,000 units IM vitamin D injection followed by 5000 units oral daily. Thyroid stimulating hormone (TSH) levels were elevated (51.4 uIU/mL; cut-off 0.3–4.2) with reduction in free T4 (0.76 ng/dL; cut-off 0.8–1.7). Thyroxin 100 μg per day was started and continued. Magnetic resonance imaging (MRI) brain and cervical cord with T1-weighted, T2-weighted, fluid attenuated inversion recovery (FLAIR) with diffusion-weighted imaging/apparent diffusion coefficient (DWI/ADC) sequence and susceptibility weighted imaging (SWI) images performed on day 7 of illness were found to be normal. Nerve conduction study performed on day 8 of illness did not reveal any lower motor neuron lesions of upper and lower limbs. Electromyogram of left biceps, extensor digitorum communis, vastus lateralis and tibialis anterior performed on day 8 of illness showed reduced interferences due to weakness with no motor unit or recruitment abnormalities and interpreted as pain induced weakness. Studies have not repeated due to limited health resource setting. Possible diagnosis of CRPS has been made according to the Budapest clinical criteria.

Patient has been treated initially with Diclofenac 50 mg twice daily and tramadol 50 mg twice daily with unsatisfactory pain relief, and subsequently treated from day 5 of illness with pregabalin 75 mg daily and methylprednisolone.

**Figure 1.** Image (a) and (b) showed initial swelling of upper and lower limb, respectively, and image (c) and (d) showed resolution of swelling during follow-up visit.
16 mg daily for 2 weeks. Regular physiotherapy was commenced from day 5 of illness in form of graded motor imagery, movement therapy, muscle strengthening and functional training. In addition, infra-red therapy to affected regions also being given during hospital stay for a week. Patient has been educated exercises to be performed at home. Review after 3 weeks at the medical clinic showed significant improvement in pain, swelling mobility, hyperalgesia and allodynia (Figure 1(c) and (d)).

Discussion
CRPS is a debilitating neurological condition manifested by predominantly pain associated with other sensory, motor, autonomic and trophic involvement.6,7 This condition usually does not follow a dermatomal pattern. The pain is usually out of proportion to the severity of the initial injury. Female gender is a risk factor for developing the disease. Studies have shown that CRPS develops following fractures, sprain and surgery including carpel tunnel syndrome. Rheumatological conditions such as rheumatoid arthritis, and vaccinations also increase risk of developing CRPS.8

There is no clear mechanism for developing CRPS. Most acceptable mechanism is thought to be a combination of risk factors starting at the time of initial injury involving nervous system sensitization, dysregulation of autonomic system and inflammatory mediator-related changes. Following an initial insult, release of pro-inflammatory mediators such as tumour necrosis factor alpha (TNF-α) and prostaglandin E2 causes nociceptor sensation and subsequently localized decreased threshold leads to hyperalgesia in these patients.9 Coupling between peripheral and sympathetic nervous systems happens over the time leads to distinct symptomatology including autonomic dysfunction of affected limb.9 Involvement of central nervous system is also an integral part of developing CRPS. Increased sensitivity of synaptic nociceptive firing in the dorsal horn had been seen following continuous peripheral nerve activation following injury.10 This reduces the threshold for response to thermal and mechanical stimuli causing allodynia.9 Immunological factors are one of the fundamental causes of developing CRPS. Release of pro-inflammatory mediators such as TNF-α, interleukin 1β (IL-1β) and interleukin-6 following increased neuropeptides leads to peripheral sensitization to the noxious stimuli.10,11 Release of cytokines and neuropeptides lead to tissue permeability and vasodilatation leads to developing oedema of the affected limb.

Viral infections including SARS-CoV-2 infection can cause nerve damage by either direct invasion of virus or secondary immune hyperactivity. Studies have shown COVID-19 infections causes small fibre neuropathy.12 Our patient’s initial presentation could be due to small fibre nerve injury following SARS-CoV-2 infection as normal standard nerve conduction study in this patient cannot rule out small fibre neuropathy. Subsequent development of hyperalgesia, and swelling of unilateral upper and lower limb are strongly indicative of a diagnosis of CRPS. There are reports of CRPS following herpes zoster infection.13 Vaz A et al.14 have reported a case of CRPS following median nerve injury caused by compression effect of hematoma during arterial line insertion in context of severe COVID infection. In contrast to our case, evidence of median nerve axonal injury has been demonstrated by nerve conduction study and hematoma has been postulated as a cause for nerve injury.14 We cannot explain reason for developing symptoms of unilateral upper and lower limb. Although there are reports of CRPS following stroke,15 this patient did not have any brain lesions in MRI to suggest a stroke.

Conclusion
This study highlights possible development of CRPS following mild COVID infection. Multidisciplinary approach is often necessary to make early diagnosis and prompt treatment. We highlighted diagnostic approaches and therapeutic modalities in form of pharmacological and physical therapy.

Acknowledgements
The authors are immensely grateful to DR V. T. Rajendran, consultant neurologist for helping us to formulate diagnosis.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical approval
Our institution does not require ethical approval for reporting individual cases or case series.

Funding
The author(s) received no financial support for the research, authorship and/or publication of this article.

Informed consent
Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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