

Neuropathic pain post-COVID-19: a case report

Matthew McWilliam,¹ Michael Samuel,^{2,3} Fadi Hasan Alkufri^{1,3}

¹Neurology, Kent and Canterbury Hospital, Canterbury, UK

²Neurology, William Harvey Hospital, Ashford, UK

³Neurology, King's College London, London, UK

Correspondence to
Dr Fadi Hasan Alkufri;
fadi.alkufri@nhs.net

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SUMMARY

A 61-year-old man with no significant medical history developed fever, headache and mild shortness of breath. He tested positive for SARS-CoV-2 and self-isolated at home, not requiring hospital admission. One week after testing positive, he developed acute severe burning pain affecting his whole body, subsequently localised distally in the limbs. There was no ataxia or autonomic failure. Neurological examination was unremarkable. Electrophysiological tests were unremarkable. Skin biopsy, lumbar puncture, enhanced MRI of the brachial plexus and MRI of the neuroaxis were normal. His pain was inadequately controlled with pregabalin but improved while on a weaning regimen of steroids. This case highlights the variety of possible symptoms associated with SARS-CoV-2 infection.

BACKGROUND

SARS-CoV-2 resulting in the COVID-19 pandemic, has been associated with a variety of extrapulmonary manifestations.¹⁻³ These presentations are varied and include cardiac, endocrine, dermatological, hepatic, gastrointestinal, renal, thromboembolic and neurological presentations. Headache, anosmia and ageusia are all common neurological symptoms of SARS-CoV-2 infection. Neuropathic pain is less frequently encountered but is also a recognised neurological symptom of SARS-CoV-2 infection.^{1,2}

We do not have consistent data regarding the prevalence and clinical characteristics of neuropathic pain in patients infected with SARS-CoV-2. It is speculated that chronic neuropathic pain may affect patients whose initial illness is less severe; however, this will require further prospective cohort studies.⁴ Neuropathic pain may considerably affect quality of life and should therefore be detected as early as possible for adequate management.

We present a case of SARS-CoV-2 associated neuropathic pain, which was refractory to neuropathic analgesia, necessitating a course of steroids.

CASE PRESENTATION

A 61-year-old man with no prior morbidity developed fever, headache and dyspnoea. He tested positive for SARS-CoV-2 (RNA detected initially with subsequent IgG detected 2 months later) and self-isolated. One week later, he started to experience a fleeting burning sensation throughout his body. Within 2 weeks, he developed tingling, numbness and burning pain in the second and third toe in one foot which spread rapidly but remained confined to both feet and both hands. There was no allodynia, skin discolouration, rash, cramps, spasms or fasciculations. The symptoms were initially intermittent

but became constant, unrelated to activity and without day or night preponderance. They interfered with his sleep and were subjectively rated 7/10 for pain severity. He reported no weakness, compromised dexterity, disequilibrium, speech or swallowing symptoms. There was no bowel or bladder dysfunction, dry mouth or eyes, disturbance of perspiration or postural hypotension. There was no history of cigarette, alcohol or recreational drug use. His neurological examination was unremarkable with no sensory loss (light touch, pain, temperature, vibration and proprioception) or ataxia. His reflexes were normal with flexor plantars. Romberg's test was negative.

INVESTIGATIONS

Initial investigations showed a mildly elevated erythrocyte sedimentation rate (ESR) of 30 mm/hour and polyclonal rise of IgM with no immune suppression, and otherwise normal full blood count, C reactive protein, renal and liver function, B₁₂, folic acid, calcium, glucose, glycated haemoglobin (HbA1C), cholesterol, vitamin D, thyroid function tests, copper, caeruloplasmin, prostate-specific antigen, antinuclear antibody, antineutrophil cytoplasm antibodies, human immunodeficiency virus (HIV) and venereal disease research laboratory test (VDRL) serology. His ESR was normal 1 month later (5 mm/hour).

MRI brain, whole spine and enhanced MRI of the brachial plexus were normal. Routine nerve conduction studies for large fibre neuropathy were normal. Somatosensory evoked potentials showed absent responses in the lower limbs, possibly due to technical reasons, with normal upper limb responses. We do not have specialised neurophysiology for small fibre testing at our institution. Skin biopsy demonstrated normal intraepidermal nerve fibre density. Cerebrospinal fluid (CSF) analysis was unremarkable for cells, protein, glucose and oligoclonal bands.

DIFFERENTIAL DIAGNOSIS

Infections can cause peripheral nervous system injury, either due to direct effects of the microbe or due to secondary immune overactivation.⁵ The temporal relationship between the SARS-CoV-2 infection and onset of limb symptoms suggests a postinfectious immune-mediated response.

A number of case reports and series from China and Europe have also reported Guillain-Barré syndrome (GBS) in association with SARS-CoV-2 infection, including demyelinating, axonal and Miller Fisher variants.⁶⁻⁸

Postinfectious neuropathic pain has been reported in the context of GBS, occurring as a result of direct IgG-induced injury of the nociceptive fibres via



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molecular mimicry.⁹ In our patient, there is no clinical or electrophysiological evidence of large fibre involvement and there was no albuminocytological dissociation of the CSF. Therefore, it is unlikely that our patient has a large fibre polyneuropathy, multiple polyradiculopathy or sensory ganglionopathy.

It is possible that he has a postinfectious autoimmune small-fibre polyneuropathy (SFN).

SFN can be defined physiologically or anatomically as a sensory neuropathy that exclusively or predominately affects small fibres and their functions. Small somatic or autonomic fibres, or both, may be involved. Patients typically present with positive sensory symptoms, including tingling, burning, prickling, shooting pain, or aching. Patients may also have negative symptoms, including numbness, 'tightness, and 'coldness'. Symptoms are usually distal and 'length-dependent,' but they are sometimes patchy or diffuse.¹⁰

Another consideration given the normal small fibre count without axonal loss or inflammation, would be primary nociceptive fibre hyperexcitability.

TREATMENT

Trials of amitriptyline (10 mg) and then nortriptyline (10 mg) were ineffective. He could not tolerate side effects on higher doses of nortriptyline (25 mg daily). An empirical course of pregabalin 25 mg three times a day was commenced with minimal benefit. Subsequent dose escalation (to 75 mg two times a day) also failed to control his symptoms prompting an 8-week prednisolone reducing regimen starting at 60 mg once a day and reducing to 0 over 6 weeks.

OUTCOME AND FOLLOW-UP

The pain score was 7/10 prior to treatment and became about 2/10 following steroid therapy. It is unclear whether this improvement can be attributed to the prednisolone or whether this simply represents the natural course of the disease. On subsequent visits, he reported intermittent burning pain and numbness in the hands and feet that increase with stress. There were no autonomic, cognitive or balance problems. He continued pregabalin 75 mg once daily regularly.

DISCUSSION

Viral infections may have a direct impact on the peripheral or central nervous system or induce a postviral immune syndrome. For example, patients with herpes zoster infection can develop postherpetic neuralgia. Enteroviruses and Human T-lymphotropic virus type 1 (HTLV1) can induce pain due to myelitis. Other viruses can cause GBS and neuropathic pain.

The exact mechanism for neuropathic pain in our patient is not known. Neuropathic pain with SARS-CoV-2 infection is not widely reported. A study from Wuhan involving hospitalised patients with SARS-CoV-2 infection reported that only 2.3% of the cohort experienced nerve pain. Of these patients 80% had severe SARS-CoV-2 infection with respiratory compromise.¹ A recent case of SARS-CoV-2-related neuropathic pain and allodynia which responded to gabapentin has been reported.² Our case differs from the above in that his respiratory manifestation of SARS-CoV-2 was mild not warranting hospital admission. There was also a brief delay in onset of his neurological symptoms, and unlike the other case his pain was not controlled with neuropathic analgesia necessitating a tapering course of steroids.

We speculate that it is possible the underlying mechanism is a postinfectious SFN. Historically, diagnosis of small fibre neuropathy has been that of exclusion of large fibre involvement, that is

the absence of any substantial large fibre involvement on neurological examination or nerve conduction study. More recently, diagnostic techniques include morphological assessment of nerve fibre density on skin biopsy and functional assessment of sensory and autonomic nerve fibres. In our patient, skin biopsy was normal. Other tests for small fibre neuropathy were not done.

Emerging data indicate that SARS-CoV-2 can trigger not only GBS but other autoimmune neurological diseases necessitating vigilance for early diagnosis and therapy initiation.¹¹ Our case highlights the array of possible SARS-CoV-2-related neurological presentations and that clinical reasoning led to effective management.

It is becoming increasingly apparent that many patients who recovered from the acute phase of the SARS-CoV-2 infection have persistent symptoms. This includes clouding of mentation, sleep disturbances, exercise intolerance and autonomic symptoms. There are Facebook groups with several thousand patients describing these symptoms. They call the illness, 'Long-Haul COVID-19' or 'Long-tail COVID-19'.¹² We are not sure if these persistent sensory symptoms are part of 'Long-Haul COVID-19'.

Learning points

- ▶ SARS-CoV-2 is associated with a variety of neurological manifestations involving both the peripheral and central nervous system.
- ▶ Neuropathic pain is an uncommon but recognised manifestation of SARS-CoV-2 infection.
- ▶ SARS-CoV-2-associated neuropathic pain may be refractory to neuropathic analgesia and warrant treatment with steroids.
- ▶ SARS-CoV-2 infection can trigger autoimmunity.

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