

Polyneuropathy following COVID-19 infection: the rehabilitation approach

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SUMMARY

A range of neurological manifestations associated with COVID-19 have been reported in the literature, but the pathogenesis of these have yet to be fully explained. The majority of cases of peripheral nervous system disease published thus far have shown a symmetrical pattern. In contrast, we describe the case of a patient with asymmetrical predominantly upper-limb sensorimotor polyneuropathy following COVID-19 infection, likely due to a multifactorial pathological process involving critical illness neuropathy, mechanical injury and inflammatory disease. His presentation, management and recovery contribute to the understanding of this complex condition and informs rehabilitation approaches.

BACKGROUND

As the coronavirus pandemic progresses, so does our understanding of the natural history, transmission and clinical presentation.¹ Although patients most commonly present with respiratory and gastrointestinal symptoms, a diverse range of symptoms have been reported. Descriptions of neurological manifestations include reports of encephalopathies, central nervous system vasculitides, cerebrovascular events and peripheral nervous system disease in particular Guillain-Barré syndrome (GBS) and its variants.²

The pathogenesis of these manifestations is yet to be fully elucidated. Evidence from other similar viruses suggests mechanisms may include direct effects of the virus on the nervous system, parainfections or postinfection immune-mediated disease as well as neurological complications of the systemic effects of COVID-19 and critical care admission.² Here, we describe the case of a patient who developed asymmetrical predominantly upper-limb sensorimotor polyneuropathy following COVID-19 infection.³

CASE PRESENTATION

The patient is a man in his 60s who first presented with severe shortness of breath. His symptoms started 12 days prior with dry cough, mild shortness of breath, fever and chest tightness. Following advice from his general practitioner, he had been self-isolating and had been commenced on Amoxicillin for suspected community-acquired pneumonia 1 day prior. On admission, he was in severe respiratory distress with saturations of 91% on 12L of oxygen, respiratory rate 34 breaths/min, temperature 37.6°C, heart rate 101 beats/min and blood pressure 163/89 mm Hg. He had a prolonged admission on intensive care requiring intubation and ventilation and later tracheostomy formation.

Throughout his intensive care admission, he had multiple SARS-CoV-2 RNA PCR tests from nasal and throat swabs and bronchoalveolar lavage samples that were negative but was treated as suspected COVID-19 based on what was deemed to be a typical clinical presentation.

He developed several complications including ventilator-associated pneumonia, gastrointestinal bleed, acute kidney injury requiring a period of haemodialysis and bilateral pulmonary embolisms. Nerve conduction studies (NCS) were carried out on day 29 of his intensive care unit admission showing evidence of widespread and severe sensory and motor axonal dysfunction, in keeping with critical care polyneuropathy.

The patient was extubated and discharged from intensive care after 55 days. He was found to have generalised weakness most prominently in the upper limbs and associated neuropathic pain. He was then transferred to a specialist multidisciplinary neurorehabilitation unit for ongoing treatment. Examination findings for the upper limbs on admission to the rehabilitation unit are shown in [table 1](#). In the lower limbs, there was 5/5 power throughout. Sensation to light touch was reduced in areas consistent with C8 and T1 dermatomes on the right, and T1 dermatome on the left. He was found to have reduced proprioception in fourth and fifth digits on the right hand. Sensation, including proprioception, was grossly normal in his lower limbs. Tone was normal in the lower limbs.

Repeat NCS ([table 2](#)) were carried out 83 days following initial admission. The study showed evidence for a peripheral neuropathy which may in part have been due to a length-dependent sensory motor axonal neuropathy; however, the striking aspect was the distribution, with profound denervation of both upper limbs and relative preservation of lower limb strength including distally with minimal axonal loss.

This pattern was not typical for a critical illness myopathy but rather raised the possibility of preferential sensory motor peripheral nerve fibre loss either affecting the lower aspect of the brachial plexus bilaterally or possibly a combination of a sensory neuropathy, in addition to perhaps a localised cervical spinal cause at the C7–T1 levels. Further investigation with MRI brachial plexus and C-spine, however, showed no focal injury or inflammation to the brachial plexus either side with minor degenerative change in the lower cervical spine only.



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Table 1 Upper limb examination findings

Movement	Power (MRC grade)	
	Left	Right
Shoulder abduction (C5)	2	2
Elbow flexion (C5, C6)	0	4
Elbow extension (C7)	3	1
Wrist extension (C6)	3	3
Wrist flexion (C8)	2	1
Finger extension (C7)	2	0
Finger flexion (C8)	0	0
Finger abduction (T1)	0	0

MRC, Medical Research Council.

DIFFERENTIAL DIAGNOSIS

Critical illness neuropathy was the proposed diagnosis to explain the initial findings in intensive care. However, repeat NCS were carried out following the acute COVID-19 infection given the asymmetry of presentation. The clinical and neurophysiological picture was atypical for this diagnosis alone with the disproportionate upper-limb involvement suggesting an additional pathological process.

Brachial plexus injury due to compression or stretch from proning has been reported, with the majority of cases recovering well.^{4 5} This likely played a contributing role to the clinical picture in the current case, the patient having been prone in intensive care. However, MRI showed no features to suggest focal injury or inflammation of either brachial plexus; that is, no pseudomeningocele to suggest traumatic nerve root avulsion, no focal collection or haematoma and no inflammatory change or thickening of the brachial plexus elements on either side. Localised cervical spine injury at the C7–T1 levels was also considered but imaging showed only minor degenerative change with no nerve root impingement.

There has been an association of asymmetric neuropathies with other viruses in particular cytomegalovirus, HIV and hepatitis C.^{6–8} However, viral screen in this case was negative and there were no other abnormal blood tests or signs suggestive of these.

Cases of GBS associated with COVID-19 have also been reported.² Differentiating the axonal variants of GBS from critical illness polyneuropathy can be difficult. The major clinical distinction is that the critical illness polyneuropathy occurs during the period of severe illness and stay in intensive care while GBS often occurs after the acute illness and leads to an

Table 2 Nerve conduction study results taken 83 days following initial admission

Sensory NCS							
Nerve /sites	Rec. site	Onset latency (ms)	PP amplitude (µV)	Velocity (m/s)			
R Median, ulnar—median ulnar orthodromic							
Median Dig II	Wrist	NR	NR	NR			
Ulnar Dig V	Wrist	NR	NR	NR			
L Median, ulnar—median ulnar orthodromic							
Median Dig III	Wrist	NR	NR	NR			
Ulnar Dig V	Wrist	NR	NR	NR			
R Radial—anatomical snuff box (forearm)							
Forearm	Wrist	NR	NR	NR			
L Radial—anatomical snuff box (forearm)							
Forearm	Wrist	NR	NR	NR			
L Sural, superficial peroneal							
Sural calf	Ankle	NR	NR	NR			
Superficial peroneal calf	Ankle	NR	NR	NR			
Motor NCS							
Nerve /sites	Muscle	Latency (ms)	Amplitude (mV)	PP amplitude (mV)	Relative amplitude (%)	Duration (ms)	Velocity (m/s)
L Median—APB							
Wrist	APB	NR	NR	NR	NR	NR	
Elbow	APB	NR	NR	NR	NR	NR	
R Median—APB							
Wrist	APB	NR	NR	NR	NR	NR	
L Ulnar—ADM							
Wrist	ADM	NR	NR	NR	NR	NR	
R Ulnar—ADM							
Wrist	ADM	NR	NR	NR	NR	NR	
R Peroneal—EDB							
Ankle	EDB	5.68	1.2	1.6	100	24.9	
Fib head	EDB	12.81	0.9	1.2	78.8	24.53	42
Pop fossa	EDB	14.53	0.6	0.9	53.1	24.64	40.7
R Tibial—AH							
Ankle	AH	4.17	5.2	7.7	100	22.24	

ADM, abductor digiti minimi; AH, abductor hallucis; APB, abductor pollicis brevis; EDB, extensor digitorum brevis; NCS, nerve conduction studies.

intensive care admission.^{9–11} Furthermore, GBS more often involves the cranial nerves. Without cerebrospinal fluid (CSF) results or serum immunological markers in this case, GBS cannot be ruled out. However, a recent epidemiological study found an overall reduction in incidence of GBS during the pandemic and while a link could not be ruled out, no epidemiological clues of SARS-CoV-2 causing GBS have been identified.¹² Given the evidence available in this case, it is more likely that the patient had a critical illness polyneuropathy.

Vasculitis¹³ and the hypercoagulable state seen in COVID-19¹⁴ leading to thrombosis within the vasa nervorum and resulting in peripheral neuropathy have been described. Proposed mechanisms relate to immune dysregulation, complement activation, clotting pathway activation or viral dissemination with direct systemic endothelial infection.¹³ Although tests for factor VIII and protein S were not carried out in this case, the patient had a D-dimer of 20733, severe acute kidney injury and persistent uraemia requiring haemodialysis, in addition to bilateral segmental and subsegmental pulmonary emboli, all of which point to excessive coagulation. This may also help to explain the patient's persistent asymmetrical polyneuropathy.

Without appropriately controlled studies, it remains unclear whether there is a causative relationship between COVID-19 and the many neurological conditions that have been cited in the literature. In addition, the mechanism of any possible causative relationship is uncertain. Based on the available evidence, it is proposed that this case is a result of a multifactorial pathological process involving critical illness neuropathy, as evidenced by the initial generalised axonal neuropathy, as well as a mechanical plexopathy best localised to the lower brachial plexus bilaterally and patchy involvement of multiple distal peripheral nerves.

OUTCOME AND FOLLOW-UP

Despite all previous swab PCR sample results returning negative, the patient had SARS CoV-2 IgG detected on a serum test carried out 100 days post admission, showing the importance of a clinical diagnosis of COVID-19. His recovery process highlights the

role of rehabilitation medicine in managing patients following COVID-19 infection. Table 3 shows the multiple functional impairments in this patient and the holistic programme to manage each aspect.

He showed improvement in impairment, activity and participation, following a period of intensive cardiopulmonary and neurorehabilitation. In addition to impairment level retraining, his rehabilitation provided him with practical ways to manage his deficits, in particular, the significant weakness in both hands (only able to extend fingers on the left). Loss of elbow flexion on the left was managed with a dynamic elbow flexion splint. A strap stylus with an environmental control system on his phone allowed him to control the TV, fan, lights and answer phone calls. The mild improvement during the subacute stage suggested that there was no active or progressive neuropathic process. Potential further improvements are thought to be possible over the next 12–18 months. Full recovery is, however, thought to be unlikely due to the extent of axonal loss and muscle wasting. He is due to be followed up by the plastic surgery team for consideration of tendon transfer surgery to allow for bicep flexion in his left arm in future, if this does not return.

DISCUSSION

Several human coronaviruses have been identified and evidence of extra pulmonary symptoms has been reported in particular with similar epidemics—SARS in 2003 and Middle East acute respiratory syndrome (MERS) in 2012. Cases describe nervous system involvement and a variety of neurological symptoms and signs.^{15 16} A *Lancet* review identified 19 publications describing cases of patients with GBS or its variants and COVID-19. The neurological presentations varied with weakness in all or some limbs with or without sensory loss, as well as cranial nerve involvement and autonomic complications.²

The majority of published cases thus far of peripheral nervous disease associated with COVID-19 have shown a symmetrical pattern. In contrast our case describes possible SARS-CoV-2-related asymmetrical polyneuropathy.

Table 3 Impairments and rehabilitation interventions

Impairment	Description	Management
Psychological	Anterograde memory loss with gaps in recall for recent events. Sleep disturbance, low mood, anxiety and trauma symptoms.	Attentional control mechanisms taught. Supported with visual imagery relaxation exercises and guided relaxation.
Cardiorespiratory	Significant reduction in exercise tolerance with desaturation to 87% oxygen saturation when walking 100m. Medical Research Council (MRC) dyspnoea 4/5.	Cardiorespiratory training cycling, squats, stairs and high knee marching with close monitoring using the Borg Rating of Perceive Exertion Scale to exercise to a moderate level of intensity. He showed improvement in saturations and MRC dyspnoea score 2 on discharge.
Speech and language	Low volume and hoarse voice.	Voice therapy techniques and swallow assessment.
Upper limb	Left hand oedema. Reduced ability to grasp using right hand and generalised upper limb weakness as described. Lack of left elbow flexion.	Intensive 10-day programme of contrast bathing, Coban wrapping and elevation. Neuromuscular electrical stimulation (on the right finger extensors to strengthen his active grasp and release now able to grasp a ball. Daily stretching and exercise regime. Dynamic elbow flexion splint and referral for consideration for tendon transfer surgery.
Function	Required complete assistance on admission for all activities of daily living.	Compensatory and adaptive methods taught to increase independence in personal tasks. A strap-stylus and environmental control system provided to allow him to control his surroundings using his phone. Fatigue management techniques were taught.
Pain management	Mechanical shoulder pain related to muscle wasting and severe neuropathic pain.	Titration of medication and trigger point injections reducing Visual Analogue Scale rating from 9/10 severity to 2/10. Upper limb sling provided to deweight his left arm and avoid further mechanical pain.
Lower limb/mobility	Generalised weakness with an inability to transfer independently or mobilise with a Rivermead Mobility Index (RMI) on admission of 7/15.	Strength and cardiorespiratory programme improving RMI on discharge to 13/15, return of lower limb power and ability to mobilise independently.

Patient's perspective

My first memories of having COVID-19 was in the intensive care unit (ICU) and being told of what I had been through, and how lucky I was. I was in the ICU for 55 days and the recovery ward for 14 days. While in the recovery ward, it was apparent to me I was in a bad way. Needing care to wash, toilet, eat, etc. I couldn't walk, transfer and sitting in a chair was very painful. While I was there, the fantastic physios told me I was going to a rehabilitation centre. A renowned place for its dedicated treatment of disabled people and I got quite emotional over this. When I got there I had a room on my own. After a week, I could walk/shuffle to the toilet. It was an awesome moment I rang everybody I knew! Progress was good, walking, physiotherapy, counselling, pain management. All done with care, dedication and brilliance of a fantastic team. I know I most likely won't have full recovery of my hands but I learnt to eat, wash and brush my teeth. Again with coaching from the team of many, I am in a good place with my recovery, although I suffer from nightmares/dreams and a bit of pain. All the tests since my stay have all been good, thanks to our brilliant National Health Service (NHS) and the support of my wonderful family.

Learning points

- ▶ Neurological manifestations of COVID-19 can be diverse, and can result in significant disability.
- ▶ Peripheral nervous system disease secondary to COVID-19 likely occurs as a result of multiple pathological processes including critical illness neuropathy, mechanical injury and inflammatory disease.
- ▶ Rehabilitation services are uniquely positioned to provide holistic management of patients suffering from the long-term complications of COVID-19 including neurological, psychological and cardiorespiratory.
- ▶ Further work is required on understanding the pathophysiology of COVID-19 associated complications and their prognosis.

The pathophysiology of the different neurological features caused by COVID-19 has yet to be fully understood. Previous studies have shown the neurotropic potential of the common human coronavirus with the presence of the virus in CSF samples of patients with multiple sclerosis.¹⁷ The effects of this may be caused either directly by the virus attacking the nervous system or due to the body's innate inflammatory immune response and requires further investigation. Awareness of the potential peripheral nervous system effects will have implications for the prognostication and rehabilitation of patients following COVID-19 infection. It is likely that different patients will require different priorities with some needing more cardiac,

respiratory, musculoskeletal or neurorehabilitation at different points in their recovery.

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