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Original article

Miller–Fisher syndrome associated with SARS-CoV-2: a case report

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ABSTRACT

SARS-CoV-2 infections are increasingly associated with neurological complications, including immune-mediated neuropathies. Miller–Fisher syndrome is a rare variant of Guillain-Barré syndrome characterised by the triad of ataxia, ophthalmoplegia and areflexia.

Here we present a case of Miller–Fisher syndrome following COVID-19 infection. The clinical presentation was a short history of a rapidly-progressive peripheral sensorimotor neuropathy with bulbar dysfunction and facial weakness following mild COVID infection. Examination revealed global areflexia and a broad-based ataxic gait. CSF analysis revealed albuminocytological dissociation and neurophysiological testing later supported the diagnosis. The patient required high flow nasal oxygen therapy for respiratory dysfunction in a level 2 care setting and received immunological treatment with intravenous immunoglobulins.

We conclude that Miller–Fisher syndrome needs to be considered in patients presenting with new sensorimotor dysfunction following SARS-COV-2 infection. Early recognition is key given the propensity to cause life-threatening respiratory failure, and early administration of immunological treatment is associated with improved prognosis.

1. Background

The SARS-CoV-2 pandemic is the largest public health emergency of our generation so far, with profound impacts across the globe. As cases continue to occur worldwide, there has been an emergence of secondary complications.

Guillain-Barré syndrome is an immune-mediated polyneuropathy which presents as an ascending sensorimotor deficit. It has long been recognised as a complication of infections, having first been recognised in 1859. The aetiology involves autoimmune molecular mimicry following the host's response to infection, resulting in myelin breakdown and axonal degeneration. The primary infection usually originates from the respiratory or gastrointestinal tract and can be bacterial or viral in origin. The most notable implicated pathogen is *Campylobacter jejuni*, with other recognised causes include *Mycoplasma pneumoniae*, *Haemophilus influenzae* and Epstein–Barr virus [1]. The Miller–Fisher variant was first described by Charles Miller Fisher in 1956. It is characterised by the triad of ataxia, ophthalmoplegia and areflexia and has been found to be associated with anti-GQ1b antibodies which target gangliosides [2].

2. Case presentation

We report the case of a 66-year-old male diagnosed with Miller–Fisher syndrome associated with SARS-CoV-2 infection. Past medical history included essential hypertension managed with atenolol, ramipril and indapamide.

Two weeks prior to admission, the patient experienced a persistent, productive cough without anosmia or dysgeusia. Community testing with nasopharyngeal PCR confirmed SARS-CoV-2 infection.

Neurological symptoms began with symmetrical paraesthesia of the hands, feet and mouth, followed by ascending lower limb weakness. On attending hospital, he was noted to have a broad-based ataxic gait and required assistance to walk. Symptoms continued to progress following admission, with sensory loss spreading to mid-shins in the lower limbs, and to mid-forearm in the upper limbs. Power loss was symmetrical with both proximal and distal weakness in upper and lower limbs (MRC Grade 4). On examination there was global deep tendon areflexia throughout the upper and lower limbs (Fig. 1).

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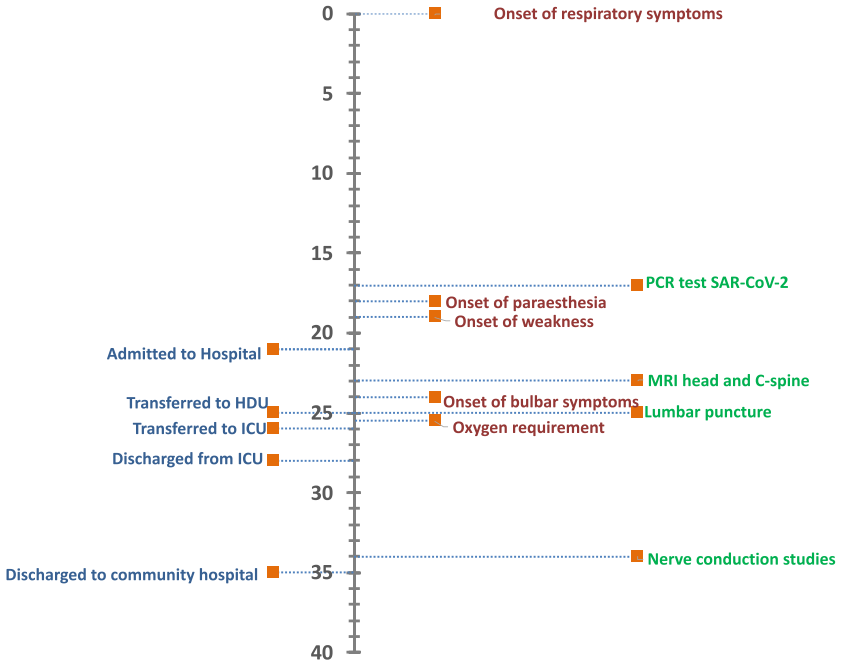

Fig. 1. Timeline to show the chronology (in days) of clinical features, investigations performed, and location of care.

Forty-eight hours into admission, the patient developed bulbar symptoms including dysarthria, dysphagia and facial paraesthesia with weakness. There was bilateral facial droop more pronounced on the left. Neurological examination revealed deficits in cranial nerves IX, X and XII, ophthalmoplegia, and a lower motor neurone VII palsy. His tongue deviated to the right on protrusion. The patient had a croaky, hoarse voice. He also described a choking sensation with swallowing, with food becoming stuck in his throat. Bedside swallow testing confirmed that he was unsafe swallowing liquids.

3. Investigations

Baseline laboratory blood tests included full blood count, liver function, renal function and bone profile. Thyroid function, haematinics, blood borne virus screening, lipid profile, γGT, ammonia and magnesium levels were also tested during admission, all of which were within reference ranges. The only laboratory investigation of note was hypokalaemia (2.7 mmol l^{-1}) at presentation, probably due to long-term diuretic therapy. Intravenous fluid with potassium was administered in the Emergency Department with no resolution of symptoms.

Baseline chest x-ray and MRI head were unremarkable. MRI of the cervical spine showed no intrinsic central cord change, but identified spondylitic changes with moderate foraminal narrowing from C3/4 to C6/7 (Table 1). Further non-contrast CT imaging after the onset of cranial nerve signs demonstrated no acute changes.

Cerebrospinal fluid (CSF) samples revealed a markedly elevated protein level (2.62) with no associated rise in white cell count (albuminocytological dissociation), along with normal red cell count and glucose levels. CSF appeared clear and no organisms were seen on microscopy or gram staining. Anti-ganglioside antibodies (GQ1B IgG and GM1 IgG) were not detected in CSF (Table 2).

Nerve conduction studies were performed at two weeks after onset of neurological symptoms. These supported the diagnosis of Guillain-Barré syndrome with low amplitude and reduced velocities in both sensory and motor nerves of the upper and lower limbs and prolongation of distal latencies (Table 3.).

Table 1
Radiology reports.

MRI head	No acute infarction, intracranial haemorrhage or mass lesion. Normal ventricles and basal cisterns. The proximal flow voids are present.
MRI cervical spine	There are spondylitic changes from C3/4 to C6/7. At C3/4 the anterior thecal sac is indented and the cord contacted but no intrinsic cord signal change at this level or elsewhere. Moderate narrowing of the left C3/4 foramen and bilaterally at C4/5 and C5/6. T4 haemangioma, otherwise unremarkable bone marrow signal.
Chest x ray	Heart and mediastinal contours are preserved. Other than faint atelectasis at the left lung base the lungs appear clear. Pleural spaces unremarkable.

Table 2
Results of lumbar puncture.

White cell count (cell/μl)	1
Red cell count (cell/μl)	22
Protein (g/l)	2.62
Glucose (mmol/l)	3.3
Gram stain	No organisms seen
Culture	No growth
Anti-Ganglioside GQ1b IgG Ab	Negative
Anti-Ganglioside GM1 IgG Ab	Negative

4. Treatment

During his hospital admission the patient developed respiratory compromise with a reduction in FVC from 1.08 to 0.57 L associated with increasing oxygen requirements. At this point he was transferred to ICU where he received high flow nasal oxygen therapy (Optiflow®, Fisher & Paykel Healthcare Limited. Auckland, New Zealand), and commenced on intravenous immunoglobulins (IVIG, Privigen®, CSL Behring UK Ltd) 0.5 mg kg^{-1} for five days. The Speech and Language Team advised appropriate oral restrictions to

Table 3
Nerve conduction studies report.

Sensory	Sensory responses from the right median and radial nerves were of low amplitude, the median responses showing moderate slowing across the wrist. Sensory responses from the right ulnar, sural and superficial peroneal nerves were absent.
Motor	Motor responses from the right median nerve show a very severe prolongation of distal latency and mild slowing in the forearm. The right ulnar nerve showed patchy slowing, particularly across the elbow in the upper arm. The right tibial nerve gave low amplitude in the foot wither severe prolongation to the distal latency and moderate slowing in the calf. The right peroneal response was normal in tibialis anterior and showed low amplitude in the foot.
Conclusion	The results are typical of Guillain Barre syndrome.

prevent aspiration. Dieticians recommended nasogastric nutrition. The patient did not require intubation, and underwent early physical rehabilitation under the care of the Physiotherapists (Fig. 1).

5. Outcomes and follow-up

A significant improvement in neurology was seen with IVIG. Facial and bulbar symptoms recovered first with almost complete recovery of function following the first dose. Peripherally, sensory function was regained earlier than motor function with upper limbs improving faster than the lower limbs. On completion of the IVIG course there was only mild residual lower limb weakness (grade 4).

The patient was discharged to a medical ward after two days in ICU, remaining an inpatient for a further fourteen days. Ongoing rehabilitation was provided by his local Community Hospital where he stayed for two weeks. On returning home he required mobility aids and a carer once daily. Community support was also provided by a Neurology Specialist Nurse. By six months he had made almost a complete recovery, with the only remaining symptoms being watering of the left eye and slight weakness of the left side of the mouth.

6. Discussion

Guillain-Barré syndrome is a rare complication of infection, occurring at a rate of around 1.1 cases per 100,000 people per year. It is a clinical diagnosis supported by ancillary investigations following exclusion of other discernible causes. The Miller–Fisher variant makes up only 1–7% of cases of Guillain-Barré syndrome. Despite current treatments, mortality from the condition is around 3–7% and recovery can be prolonged with ongoing severe disability in 14% of patients after one year [1,3].

Management is two-fold with immunological treatment and supportive care. Early administration of IVIG or plasma exchange is associated with improved long-term prognosis. Respiratory muscle weakness necessitates frequent monitoring with spirometry and early involvement of ICU. Mechanical ventilation is recommended when FVC falls below 20 mL kg^{-1} [4,5] and is required in around 20–30% of cases [1,5]. In this case, the patient received Level 2 care but mechanical ventilation was not required and symptoms improved rapidly with IVIG.

Both Guillain-Barré syndrome and Miller–Fisher syndrome associated with SARS-CoV-2 have been reported [6–10]. This case was notable as it highlighted that Miller–Fisher syndrome can occur following relatively mild cases of COVID and in the absence of the classical chemosensory disturbances (anosmia or ageusia). This case also helps outline the timeframe over which events occur in Miller–Fisher syndrome following COVID, with neurology developing two weeks after onset of respiratory symptoms. Other reported cases describe development of neurology earlier on following the initial infection [8–10] and as far as we are aware this is the longest documented time between antecedent infection and development of Miller–Fisher syndrome following mild Sars-CoV-2 infection. Guillain-Barré syndrome has been reported up to four weeks after the antecedent infection [1]. This is of importance as viral detection by PCR from nasopharyngeal swabs decreases with time [11] raising the possibility of the development of immunological complications in the absence of positive PCR testing. Indeed the above patient had a negative PCR test at the time of admission to hospital, suggesting the pathophysiology of the condition was being driven by immunological mechanisms and not the virus itself. This may also have implication in the use of immunosuppressive agents as part of the therapeutic management of COVID, such as IL-6 inhibitors and the emerging antibody treatment which could be hypothesised in preventing of immunological complications as well as benefiting the primary viral infection.

A number of differential diagnoses for the initial sensorimotor disturbance were considered. The patient did not have diabetes mellitus, a significant alcohol history or any neurological family history, and the rapid onset of symptoms suggested these to be unlikely causes. Early imaging of the patient's brain with MRI excluded a central pathology. Whilst changes were noted on the MRI C-spine, these were chronic in nature and inconsistent with the distribution of neurology. The evolving clinical picture of ascending paralysis with facial weakness with CSF albuminocytological dissociation suggested Miller–Fisher syndrome. This was supported by the rapid clinical improvement with IVIG therapy and later neurophysiology testing. The monophasic clinical course of the disease is also a core feature of Guillain-Barré syndrome. The nadir of neurological weakness should be reached between 12 h and 28 days; in this case this was at eight days, although the full extent of symptoms may not have been reached, halted by immunological therapy. Whilst anti-ganglioside antibodies were not detected in CSF, they lack specificity and can be negative in up to 15% of cases [2]. Indeed the GBS classification group state that whilst informative, serological testing is not a requirement for the diagnosis of Miller–Fisher syndrome [12]. The antecedent infection was considered most likely to be SARS-COV-2 infection given the temporal sequence of events. *Campylobacter* serology was negative. The two-week interval between infection and development of neurological symptoms fitted with an autoimmune process, as opposed to a primary complication of the virus itself. Once considered single entities, Guillain-Barré syndrome and its variants are now recognised to form a spectrum of disorders. Variability in clinical features between these discrete but overlapping subtypes can present a nosological challenge in reaching a precise diagnosis. The GBS Classification group have devised diagnostic criteria emphasising focus on clinical presentation [12]. More recently, polyneuritis cranialis has been considered as a separate diagnosis within the GBS-MFS interface [13] with post-infective cranial neuropathies in the absence of ataxia and other cardinal features of MFS. Incomplete forms of Miller–Fisher syndrome have also been recognised in the absence of one of the cardinal features. In this case it was felt the diagnosis fitted best with Miller–Fisher syndrome, displaying the classical triad (ataxia, areflexia, ophthalmoplegia). Consciousness was preserved with no hypersomnolence excluding CNS subtypes such as Bickerstaff-brainstem-encephalitis. Localised forms of GBS such as pharyngeal–cervical–brachial weakness were also considered less likely as four-limb weakness was present from the outset and more predominant in the lower limbs.

SARS-CoV-2 is an emerging infection, the full scope of which is not yet fully understood. Secondary complications are increasingly being recognised. There has been much awareness over 'long-COVID', a condition similar to chronic fatigue syndrome [14]. Other documented neurological complications include mononeuropathies

[15] and transverse myelitis [16]. Post-infectious immune-medicated neuropathy is a rare but well recognised as a complication of infections, so perhaps it should come as no surprise that cases associated with COVID infection are emerging.

7. Conclusions

We conclude that Miller–Fisher syndrome, needs to be considered in patients presenting with sensorimotor dysfunction following SARS-COV-2 infection, including up to two weeks following the infection. Early recognition of this neurological emergency is key given its propensity to cause life threatening respiratory failure and with early administration of immunological therapy associated with improved prognosis. The SARS-CoV-2 pandemic has already been associated with considerable morbidity and mortality from the primary infections and the multitude of emerging complications will continue to add to the widespread effects of the pandemic.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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