Case report

**Guillain-Barré syndrome presenting with COVID-19 infection**

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SUMMARY

A construction worker in his 30s presented three times in 4 days with progressive upper and then lower limb weakness. On the first two occasions he had no systemic symptoms, but on the third presentation he had fever and cough, starting from day 4 of weakness. Examination identified weakness in all four limbs and areflexia, suggesting a peripheral neuromuscular disorder. Investigations were consistent with Guillain-Barré syndrome and additional COVID-19 (SARS-CoV-2) infection. The patient improved after immunoglobulin treatment. At least four cases of Guillain-Barré syndrome have been reported in the literature with concurrent COVID-19 illness in whom respiratory signs appeared a few days after the onset of neurological signs. With the incubation period for COVID-19 respiratory symptoms believed to be up to 14 days, it is possible that neurological symptoms could develop before respiratory and other symptoms. During the current pandemic, presence of concurrent COVID-19 infection needs to be considered in patients presenting with Guillain-Barré syndrome.

BACKGROUND

The recent outbreak of COVID-19 (SARS-CoV-2) became an international pandemic in a short space of time. The majority of patients with COVID-19 infection demonstrate fever and respiratory illness. Here, we report a case of a patient with COVID-19 who presented with Guillain-Barré syndrome.

CASE PRESENTATION

We report the case of a Georgian construction worker in his 30s who presented to the emergency department having developed numbness in his hands the day before, and now with hand weakness, making it difficult to squeeze a lemon, followed by subjective leg weakness. On examination, power was Medical Research Council (MRC) grade 4/5 in his dominant left leg weakness. On the third presentation he had fever and cough, starting on day 4, unable fully to lift his arms and with difficulty standing. He was normally fit and well and was taking no medications. He had no history of recent illness, no spinal pain and no sphincter disturbance. He had experienced regular epistaxis for over 2–3 weeks which had not occurred since childhood. He lived with his partner, was an ex-smoker and had travelled to Latvia for Christmas 3 months before and to Prague 4 weeks before, with a brief change in bowel habit. There had been no insect bites. He had already decided to stop work on the day the weakness started as he was worried there was insufficient social distancing on-site to protect against COVID-19. He was worried that the weakness was due to thyroid dysfunction, of which he had a family history.

Examination identified a temperature of 38.3°C, blood pressure of 174/110 mm Hg and heart rate of 101 beats per minute. There was no facial weakness, but there was symmetrical limb weakness, with an MRC grade of 3/5 for shoulder abduction, 4/5 for wrist dorsiflexion, 2/5 for finger extension, 3/5 for hip flexion, 3/5 for ankle dorsiflexion and 4/5 for ankle plantar flexion. He was areflexic with downgoing plantar responses. Vibration, joint position sense, temperature and light touch sensation were all intact. Forced vital capacity (FVC) was 4.7 L (85% predicted).

He was admitted with suspected COVID-19 infection and potential Guillain-Barré syndrome.

INVESTIGATIONS

Urea and electrolytes, liver function tests, thyroid function tests and creatine kinase were normal. Total white cell count and C-reactive protein were initially normal. There was lymphopaenia of 0.81 × 10^9/L (reference range 1.0–4.5 × 10^9/L), raised monocyte count of 1.02 × 10^9/L (reference range 0.2–0.8 × 10^9/L), patchy perihilar airspace shadowing on chest X-ray and COVID-19 RNA was positive on nasal and throat swab. His 12-lead ECG showed mild first-degree heart block of 220 ms PR interval, while echocardiogram was unremarkable.

Lumbar puncture yielded cerebrospinal fluid (CSF) with white cell count <0.001 × 10^9/L (<1/mm^3), protein 1.15 g/L (reference range 0.15–0.45 g/L), CSF glucose 3.3 mmol/L and plasma glucose 5.3 mmol/L (normal CSF glucose approximately two-thirds the plasma glucose). Herpes simplex virus types 1 and 2 on X-ray. He was discharged home with advice to return if required.

He came for the third time to the emergency department 2 days later, day 5 of weakness, this time with cough and fever starting on day 4, unable fully to lift his arms and with difficulty standing. He was normally fit and well and was taking no medications. He had no history of recent illness, no spinal pain and no sphincter disturbance. He had experienced regular epistaxis for over 2–3 weeks which had not occurred since childhood. He lived with his partner, was an ex-smoker and had travelled to Latvia for Christmas 3 months before and to Prague 4 weeks before, with a brief change in bowel habit. There had been no insect bites. He had already decided to stop work on the day the weakness started as he was worried there was insufficient social distancing on-site to protect against COVID-19. He was worried that the weakness was due to thyroid dysfunction, of which he had a family history.

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DNA, varicella zoster virus DNA, enterovirus RNA and COVID-19 RNA were not detected in CSF.

Serum antiganglioside antibodies, antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), hepatitis B, hepatitis C, HIV, syphilis, cytomegalovirus IgM, Epstein-Barr virus IgM, Mycoplasma IgM tests and Lyme disease serology were negative, as were urinary Legionella and pneumococcal antigen tests. Stool samples were not taken.

Nerve conduction studies were not performed initially due to coronavirus restrictions, but were performed 4 weeks after the onset of weakness. These showed the following:
- All recorded motor responses were low in amplitude in both the upper and lower limbs, supporting axonal loss, proximal greater than distal. For example, right tibial nerve response amplitude when stimulated at the popliteal fossa was 1.0 mV and at the ankle was 2.1 mV (tibial nerve amplitude normal at ≥4 mV).
- All recorded motor conduction velocities were borderline slow, for example, the conduction velocity of the right tibial nerve segment from popliteal fossa to ankle was 39 m/sec (normal ≥41 m/sec).

(Normal values given will vary with age, height and temperature.)

**DIFFERENTIAL DIAGNOSIS**

Differential diagnoses included acute pathologies of the nerve roots (radiculopathies), brachial and lumbosacral plexuses, peripheral nerves, neuromuscular junctions and muscle, with conditions including Guillain-Barré syndrome, plexopathies, vasculitic neuropathy and Lyme disease (prevalent in Latvia). The sensory symptoms and normal creatine kinase pointed away from a muscle disorder. The history, the symmetry on examination and CSF analysis were typical of Guillain-Barré syndrome or Lyme polyradiculoneuritis, with albuminocytological dissociation (high CSF protein with normal cells). Nerve conduction studies supported a motor process affecting the axons both in the roots and nerves: a motor polyradiculoneuropathy. Negative Lyme serology gave a diagnosis of acute motor axonal neuropathy subtype of Guillain-Barré syndrome.

**TREATMENT**

Intravenous immunoglobulins were given at 0.4 g/kg/day for 5 days. FVC and limb power were closely monitored. Subcutaneous low molecular weight heparin was given, particularly important in this patient with an increased risk of thrombosis from both lower motor neurone syndrome and COVID-19, which can result in a hypercoagulable state. The patient received daily physiotherapy, focusing both on respiratory and physical function.

**OUTCOME AND FOLLOW-UP**

Following immunoglobulin therapy, the patient showed significant improvement, with power in all limb muscle groups in the range MRC grade 4−/5 to 4+/5. He remained areflexic with no sensory nor autonomic disturbance, except for the prolonged PR interval. Post-treatment FVC was 4.9 L (89% predicted).

The patient was discharged from the hospital after a stay of 12 days, able to mobilise with residual weakness predominantly in his hands and feet. He chose to go straight home rather than stay in intermediate care. He was reviewed in the neurology clinic 2 weeks after discharge. Power was restored except for MRC grade 4+/5 for finger extension and abduction in his non-dominant right hand, 3/5 for the left great toe dorsiflexion and 4+/5 for dorsiflexion of the left toes. He was able to stand on his toes but not on his heels, and walking was mildly affected. Reflexes were now present and there remained no sensory signs.

He was able to return to work 6 weeks after admission, but remained affected with intermittent chest pain and shortness of breath on going upstairs.

**DISCUSSION**

Guillain-Barré syndrome is preceded by infection or other immune stimulus such as vaccination which induces an autoimmune response targeting the nervous system, in this case the spinal roots and peripheral nerves. It is characterised by progressive weakness and areflexia, with pain preceding weakness in one-third of adult patients. Subtypes include demyelinating types, in which the affected myelin sheath causes aberrant conduction, and the axonal forms affecting the axons themselves.

This case highlights the difficulty of diagnosing Guillain-Barré syndrome as a case of subacute weakness, when in a typical district general hospital covering 400 000 people we might expect 4–8 cases per year (1–2 per 100 000 population per year). The patient presented to the hospital three times before a diagnosis of Guillain-Barré syndrome was considered. There was neither facial weakness nor spinal pain to point towards the diagnosis.

Also highlighted is that evaluation of weakness based on loss of function can be more sensitive than physical examination: no lower limb weakness was identified on examination despite the patient having difficulty standing from a chair. It is invaluable to record one or two reflexes in both the upper and lower limbs in any patient with subjective weakness to alert the clinician to a potential upper or lower motor neurone disorder and as a baseline for future examination. Recording of reflexes on prior attendances may have shortened the time to diagnosis.

This case raises the issue of whether the concurrent COVID-19 infection was a coincidence or could have been related to the Guillain-Barré syndrome. COVID-19 is a disease caused by a newly emergent virus species of the Betacoronavirus genus, other species of which have caused the common cold, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).

The new virus has been called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has been identified as the cause of an outbreak of a respiratory illness that originated in Wuhan City, Hubei Province, China, in December 2019.4 The WHO named the disease ‘coronavirus disease 2019’ (COVID-19) and in March 2020 declared the COVID-19 outbreak a pandemic.

SARS-CoV-2 has similar characteristics to SARS and MERS coronaviruses. Species of Betacoronavirus genus are known to be potentially neuroinvasive. Previously MERS was found to be associated with Guillain-Barré syndrome in two patients. Neurological manifestations associated with COVID-19 include stroke, impaired consciousness and encephalopathy.

There have been at least 12 cases reported in the literature as of 2 May 2020 linking Guillain-Barré syndrome with SARS-CoV-2 (COVID-19). As with our patient, four of these cases had signs of Guillain-Barré syndrome at initial presentation. UK-wide surveillance via notification portals identified three confirmed cases of Guillain-Barré syndrome reported from 2 April 2020 to 26 April 2020, of which this patient was one. Our patient developed signs of Guillain-Barré syndrome before COVID-19 respiratory symptoms started on day 4 of weakness. The question is posed whether this could be a parainfectious phenomenon, due to direct neuroinvasion by the virus. Or could it be postinfectious with the incubation period for respiratory symptoms overlapping that for immune-mediated neurological symptoms? Guillain-Barré syndrome usually follows an immune stimulus from day 1 to 4 weeks later. Possible causes of the
case presented here are the bowel disturbance in Prague 4 weeks before and the SARS-CoV-2 infection. It is intriguing that the length of the presymptomatic phase of SARS-CoV-2 before respiratory symptoms (the incubation period) is up to at least 14 days.

Patient's perspective

First of all I would like to thank all nurses and doctors who took care of me in Southend Hospital. The whole experience was scary because obviously nothing like this has ever happened to me. I agree with what’s said in the report regarding accepting and examining patients coming to A&E – I was only admitted and treated only the 3rd time I came to hospital. However, the care I received after that was brilliant and it was re-assuring to hear stories from a doctor who had suffered GBS before. He told me everything will be as it was. This was a stressful time for me and my family and I am still not 100% recovered, but have started to go to work (around 1.5 months after first symptoms) and am expected to make full recovery. Thank you again.

Learning points

► Consideration of function as well as physical examination of power to determine the location of weakness are important.
► Examining reflexes and checking for plantar responses in any patient with weakness are also important.
► With the backdrop of the COVID-19 pandemic, the presence of a concurrent COVID-19 infection needs to be considered in patients presenting with symptoms and signs of Guillain-Barré syndrome.
► If neurological manifestations of COVID-19 infection could appear before respiratory symptoms, it would be of utmost importance to use effective personal protective equipment, in particular for aerosol-generating procedures such as spirometry, in patients presenting with Guillain-Barré syndrome.

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