COVID-19 Associated Parainfectious Encephalomyelitis: A Unique Case with Early CNS Immunological Response and Practical Implications

Sir,
A 62-year-old male, known diabetic for 4 years presented with a history of fever, cough, and dyspnoea for 3 days. Examination at admission showed that he had tachycardia (HR 120/min) and tachypnea (30 breaths/min) and was febrile (102°F). Other than fine basal crepitations, systemic examination was unremarkable. Arterial blood gas analysis revealed hypoxemia (pO2 61 mm Hg on room air). A nasopharyngeal swab collected and sent for RT-PCR for SARS-CoV-2 was positive (Ct value: E: 31.1; S gene: 30.7). Real Star SARS-CoV-2 RT-PCR kit, altona Diagnostics GmbH, Hamburg, Germany. Laboratory investigations showed hemoglobin 14.6 gm%, total leukocyte count 14,500/mm³ with lymphopenia, creatinine 1.73 mg%, lactate dehydrogenase 428 IU/L (Ref: 225–460 IU/L), ferritin 816 ng/ml (Ref: 20–300 ng/ml), D-dimer 15,840 ng/ml (Ref: <500 ng/ml), and C reactive protein 24 mg/L (Ref: <3 mg/L). Chest X-ray showed bilateral peripheral and subpleural interstitial infiltrates. He was initiated on supportive management with oxygen in view of hypoxemia with dexamethasone and heparin. On day 2 of admission (day 4 post-illness onset), on waking up in the morning, he was unable to move both lower limbs with impaired sensation below the waist. Examination showed neck flexor weakness with flaccid paraplegia (MRC Grade 0) and absent proprioception in bilateral lower limbs with urinary retention. On day 3 (day 5 post-illness onset), he progressed to develop dysphonia, dysphagia, nasal regurgitation, and worsening dyspnoea with pooling of secretions.

Contrast enhanced magnetic resonance imaging of brain and cervico-dorsal spine [Figure 1a and b] showed longitudinally extensive myelitis extending from C6 level to the conus without enhancement. There were T2 hyperintensities with faint peripheral contrast enhancement involving the midbrain, pons, and left middle cerebellar peduncle [Figure 1c–f]. Cerebrospinal fluid (CSF) analysis showed 28 cells (polymorphs 11%, lymphocytes 88%, RBC 130) with protein 173 mg% and glucose 159 mg%. The CSF was transferred into sterile tubes without viral transport medium. The CSF postsampling was immediately placed in a cold container and transferred immediately to the laboratory with adequate maintenance of cold chain. The CSF tested with an in-house real-time RT-PCR assay (CDC N1/N2 assay) targeting the nucleoprotein (N) gene of SARS-CoV-2 was negative. The assay used for viral RNA detection was validated with appropriate positive, negative, and internal controls (GAPDH). Multiplex real-time PCR for viruses (HSV1, HSV2, VZV, CMV, EBV, and adenovirus) and all CSF cultures (bacterial, fungal, and tuberculosis) were negative. Cytology did not reveal any atypical cells. The serum interleukin-6 (IL-6) level was 11.6 pg/ml (Ref: <7 pg/ml) and CSF IL-6 level was 2762 pg/ml (chemiluminescence method). Serum autoimmune markers (myelin oligodendrocyte glycoprotein and aquaporin 4 antibodies) were negative. Antinuclear antibody and complements (C3, C4) were negative.

CSF (day 5 post-illness onset) tested for antibodies to SARS-CoV-2 Spike Receptor Binding domain (RBD) (Siemens ADVIA Centaur COV2T and COV2G kits for total and IgG antibody) and nucleoprotein (N, Roche Elecsys Anti-SARS-CoV-2) showed a reactivity rate of 5.19 for total anti-RBD antibody (sample/cutoff ratio; positive >1.0), 4.62 for anti-RBD IgG antibody, and 3.8 for anti-N IgG antibody. Neutralizing antibodies tested using a SARS-CoV-2 surrogate strains for anti-RBD IgG antibody, and 3.8 for anti-N IgG antibody. Neutralizing antibodies tested using a SARS-CoV-2 surrogate

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5. Ramanathan S, O'grady GL, Malone S, Spooner CG, Brown DA, Gill D, et al. Neutralizing antibodies tested using a SARS‑CoV‑2 surrogate swab collected and sent for RT‑PCR for SARS‑CoV‑2 was positive (Ct value: E: 31.1; S gene: 30.7; Real Star SARS‑CoV‑2 RT‑PCR kit, altona Diagnostics GmbH, Hamburg, Germany). Laboratory investigations showed hemoglobin 14.6 gm%, total leukocyte count 14,500/mm³ with lymphopenia, creatinine 1.73 mg%, lactate dehydrogenase 428 IU/L (Ref: 225–460 IU/L), ferritin 816 ng/ml (Ref: <3 mg/L). Chest X‑ray showed bilateral peripheral and subpleural interstitial infiltrates. He was initiated on supportive management with oxygen in view of hypoxemia with dexamethasone and heparin. On day 2 of admission (day 4 post‑illness onset), on waking up in the morning, he was unable to move both lower limbs with impaired sensation below the waist. Examination showed neck flexor weakness with flaccid paraplegia (MRC Grade 0) and absent proprioception in bilateral lower limbs with urinary retention. On day 3 (day 5 post-illness onset), he progressed to develop dysphonia, dysphagia, nasal regurgitation, and worsening dyspnoea with pooling of secretions.

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The septicemia and pulmonary infiltrates for which antibiotics were started as per sensitivity. On day 14 (day 16 post-illness onset), he had a sudden cardiac death attributable to pulmonary embolism or a cardiac arrhythmia from which he could not be revived. There was no autonomic dysfunction noted during the clinical course. The patient was not receiving any arrhythmogenic drugs including hydroxychloroquine.

COVID-19 neurological manifestations including olfactory–gustatory dysfunction, encephalopathy, strokes, and postinfectious acute disseminated encephalomyelitis (ADEM) are being increasingly reported. The pathogenesis includes direct viral invasion either through the olfactory tract or viremia with a breach in the blood brain barrier associated with a robust proinflammatory immune response mediated by IL-1, IL-6, and TNF-α leading to glial cell activation and/or antiglial antibody production triggered by the virus antigen. Autoimmune responses get activated by mechanisms of molecular mimicry and bystander activation.

There have been multiple reports of acute necrotizing encephalomyelitis associated with COVID-19. The copresentation of neurological complications with respiratory symptoms early in the disease, with an intense virus-specific intrathecal antibody response, and markedly elevated CSF IL-6 levels is unique in this patient. This is highly suggestive of a predominant CNS immune response being causal as opposed to a systemic immune response with blood brain barrier dysfunction resulting in demyelination, as is classically postulated in postinfectious ADEM. A superadded vascular etiology for the myelopathy was also considered in view of the COVID-19 associated prothrombotic state.

Antibody responses to SARS-CoV-2 have been reported to occur early in a subset (30%) as early as 3–7 days after symptom onset. But more importantly, Ho et al. reported patients with severe SARS with early and high antibody responses. This was attributed to cross-reacting antibodies with non-SARS coronaviruses. The phenomenon of “antibody-dependent enhancement” of opsonized virus particles by binding of IgG antibody to Fcy receptors on mononuclear cells, causing potentiation of infection and release of proinflammatory cytokines, may also be a contributory factor in this case. While seasonal CoV antibodies were not tested for in this patient, the strength of the immune response early in the disease provide supporting evidence to this phenomenon.

In the context of parainfectious early ADEM, where there could be concomitant viremia, antivirals like Remdesivir can also be ideally included in the treatment regimens in addition to anti-inflammatory agents. However, this case manifested quite early in the pandemic when there were no specific antivirals recommended as standard of care. This patient presented to us during the initial stages of the pandemic, when the evidence for use of Tocilizumab was still evolving, and was restricted to case reports. Hence, it was not considered.

Superinfection and thrombotic complications in the setting of severe neurological comorbidity interfere with both optimal immunomodulation and are implicated in the adverse prognosis seen in these parainfectious cases. Considering the low sensitivity of CSF real-time RT-PCR, demonstration of antibodies against SARS-CoV-2 could be a useful, early diagnostic marker. Prospective studies looking specifically at the correlations between disease activity and CSF biomarkers could provide valuable insights into pathogenesis and help evolve targeted therapies as well strategies for vaccine development.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other

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**Figure 1:** Magnetic resonance imaging showing longitudinally extensive myelitis from C6 to conus (a, b). Brain imaging revealing T2 hyperintensity involving pons and left middle cerebellar peduncle (c) with patchy restricted diffusion (d, e) and faint peripheral contrast enhancement (f).
clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**
There are no conflicts of interest.

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