SARS-CoV-2 Encephalitis Presenting as a Clinical Cerebellar Syndrome

A Case Report

Katryn Oosthuizen, MBChB, Elizabeth Christina Steyn, MBChB, Lawrence Tucker, MBChB, MSc, FCP(SA), PhD, Innocent Vusumusi Ncube, MBChB, FC Rad (Diag) MMed, Diana Hardie, MBChB, MMedPath, and Suzaan Marais, MBChB, FC Neurol(SA), PhD

Correspondence
Dr. Marais
marais.suzaan@gmail.com

A 52-year-old previously healthy man was hospitalized with a 6-day history of progressive gait instability rendering him unable to walk. He reported no respiratory symptoms or fever. He was a smoker (5–10 pack-years) and consumed an undisclosed amount of alcohol over weekends for some years. At presentation, he was tachypneic (20 bpm) and pyrexial (37.7°C) but alert and oriented. He exhibited cerebellar signs, including multidirectional gaze-evoked nystagmus, dysarthria, and truncal and appendicular ataxia. His examination was otherwise normal.

Nasopharyngeal real-time polymerase chain reaction (RT-PCR) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing was negative and chest radiograph showed nonspecific coarse bronchovascular markings. Uncontrasted CT brain revealed a central midbrain hypodensity but MRI was delayed due to resource constraints. Routine blood analyses were normal, apart from neutrophil predominant leukocytosis (17 × 10⁹/L) and elevated erythrocyte sedimentation rate (72 mm/h). CSF analysis revealed pleocytosis (lymphocytes: 49/μL, polymorphonuclear cells: 2/μL) and increased immunoglobulin G index (0.62; normal ≤0.6); protein (0.37g/L), albumin (157 mg/L), and glucose (3.6 mmol/L) were normal. Tests for infections and malignancy were negative (e-Results, data available from Dryad: doi.org/10.5061/dryad.pk0p2ngm7). Due to his alcohol use, thiamine (500 mg/d) was initiated.

The patient’s ataxia improved marginally, but on day 7, he became severely agitated, lacked insight, and displayed fluctuating orientation. EEG was normal. Behavioral abnormalities were unresponsive to benzodiazepines and antipsychotics (olanzapine: 7.5 mg/5 mg twice daily). MRI brain showed features consistent with brainstem encephalitis (figure, A–E). Corticosteroid therapy was delayed due to concern of increasing agitation and IV immunoglobulin was not offered as his behavior precluded IV therapy without prolonged physical restraint. Normal or negative blood investigations included tumor markers, infection and vasculitis screening, and autoimmune antibodies (e-Results, data available from Dryad: doi.org/10.5061/dryad.pk0p2ngm7). Serum screening for onconeural antibodies was positive for amphiphysin. Repeat CSF analysis on day 14 was normal. CT chest, abdomen, and pelvis identified no malignancy but revealed nonspecific ground-glass opacifications in lung periphery (figure, F) commonly seen in COVID-19 pneumonia.¹

On day 17, respiratory RT-PCR testing for SARS-CoV-2 and serum SARS-CoV-2 antibodies were positive. Retrospective analyses of samples collected on admission detected SARS-CoV-2 RNA by RT-PCR in CSF (e-Results, data available from Dryad: doi.org/10.5061/dryad.pk0p2ngm7); SARS-CoV-2 antibodies were negative in serum. Behavioral abnormalities persisted until prednisone (1 mg/kg/d) initiation but improved dramatically thereafter. Ataxia continued improving.

At discharge on day 36, the patient was walking independently. Mild emotional lability persisted. Six months later, repeat CSF examination remained normal (e-Results, data available from Dryad: doi.org/10.5061/dryad.pk0p2ngm7); contrasted CT chest and whole-body ¹⁸F-FDG PET/CT

From the Division of Neurology, Department of Medicine (K.O., E.C.S., L.T., S.M.), Department of Radiology (I.V.N.), and Division of Virology, Department of Microbiology (D.H.), Groote Schuur Hospital and University of Cape Town; and Neurology Research Group (K.O., E.C.S., L.T., S.M.), UCT Neuroscience Institute, University of Cape Town, South Africa.

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showed patchy postinfectious parenchymal lung changes, but no features of malignancy; and the previous MRI brainstem abnormalities had resolved (figure, G–I). At this time, all medication had been discontinued. The patient’s mental state had normalized, but he exhibited mild residual cerebellar signs including dysarthria, appendicular ataxia, and a wide-based gait.

Discussion

Our patient meets case definition criteria for confirmed SARS-CoV-2 encephalitis, with evidence indicating neurologic manifestations occurring during acute infection. Detection of SARS-CoV-2 in CSF but not nasopharyngeal swab may reflect poor swab technique or, alternatively, a compartmental response with higher viral loads in CNS compared to upper airway during early disease. Cerebellar ataxia in patients with COVID-19 is increasingly described, but SARS-CoV-2 has rarely been detected in CSF of previous cases tested, potentially reflecting sample collection timing or different pathogenic mechanisms.

Although initial examination suggested pancerebellar dysfunction, imaging abnormalities were confined to the brainstem. Several reports have similarly shown clinical–radiologic disconnect in patients with COVID-19 with cerebellar signs, with MRI showing no abnormalities, or abnormalities located exclusively outside the cerebellum.
Findings in our patient likely reflected involvement of brainstem–cerebellar connections, although additional direct cerebellar involvement cannot be excluded. COVID-19 encephalitis may occur through direct viral damage, host immune responses, or a combination of factors.2 Immunotherapies are used to treat postinfectious immune-mediated conditions.2 However, treatment of COVID-19 encephalitis during acute infection is controversial. Immunotherapies administered during active infection could potentially diminish the patient’s antiviral response, exacerbating CNS disease. It is possible that SARS-CoV-2 directly caused neural dysfunction, given viral detection in CSF. However, the encephalopathy responded favorably to corticosteroids, suggesting host immune mechanisms contributed to disease pathogenesis.

The clinical significance of anti-amphiphysin antibodies was unclear given that no malignancy was identified. An association between viral infections and antibodies against cell surface antigens is well-documented. For example, herpes simplex encephalitis can trigger anti-NMDAR encephalitis, potentially through uncovering epitopes resulting in antibody responses.5,7 The possibility that SARS-CoV-2 encephalitis can induce responses against amphiphysin, an intracellular synaptic antigen, is intriguing and should be explored in future studies.7

This report contributes to the rapidly expanding knowledge base of COVID-19–associated neurologic syndromes and highlights uncertainties regarding the pathogenesis of cerebellar dysfunction in, and optimal management of, patients with COVID-19–associated encephalitis.

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**Appendix Authors**

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<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
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<tr>
<td>Katryn Oosthuizen,</td>
<td>University of Cape Town,</td>
<td>Major role in acquisition of data,</td>
</tr>
<tr>
<td>MBChB</td>
<td>South Africa</td>
<td>drafted the manuscript for intellectual content.</td>
</tr>
<tr>
<td>Elizabeth Christin</td>
<td>University of Cape Town,</td>
<td>Major role in acquisition of data,</td>
</tr>
<tr>
<td>Steyn, MBChB</td>
<td>South Africa</td>
<td>drafted the manuscript for intellectual content.</td>
</tr>
<tr>
<td>Lawrence Tucker,</td>
<td>University of Cape Town,</td>
<td>Major role in acquisition of data,</td>
</tr>
<tr>
<td>PhD</td>
<td>South Africa</td>
<td>revised the manuscript for intellectual content.</td>
</tr>
<tr>
<td>Innocent Vusumusi</td>
<td>University of Cape Town,</td>
<td>Interpreted the data, revised the manuscript for intellectual content.</td>
</tr>
<tr>
<td>Ncube, FC Rad (diag)</td>
<td>South Africa</td>
<td></td>
</tr>
<tr>
<td>Diana Hardie,</td>
<td>University of Cape Town,</td>
<td>Major role in acquisition of data,</td>
</tr>
<tr>
<td>MMedPath</td>
<td>South Africa</td>
<td>interpreted the data, revised the manuscript for intellectual content.</td>
</tr>
<tr>
<td>Suzaan Marais,</td>
<td>University of Cape Town,</td>
<td>Designed and conceptualized the study, analyzed the data,</td>
</tr>
<tr>
<td>PhD</td>
<td>South Africa</td>
<td>drafted the manuscript for intellectual content.</td>
</tr>
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**References**


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