

Parkinsonism as a Sequela of SARS-CoV-2 Infection: Pure Hypoxic Injury or Additional COVID-19-Related Response?

The role that SARS-CoV-2 infection could play in causing post-COVID-19-parkinsonism (even to the point of creating a modern pandemic of post-infectious parkinsonism) has gained significant traction since the virus first emerged.^{1,2} One year later, however, there have been only five published cases of parkinsonism occurring in the setting of COVID-19.³⁻⁷ Although the clinical features of one of these cases is highly suggestive of a parainfectious/inflammatory etiology,⁴ many of the other presentations may merely represent an infectious stressor unmasking prodromal Parkinson's disease.^{7,8} We present an alternative cause of parkinsonism following SARS-CoV-2 infection.

A 46-year-old man presented with fever, dyspnea, and cough. He was diagnosed with COVID-19 and rapidly became hypoxicemic, developing acute respiratory distress syndrome necessitating intubation and ventilation. He became hypotensive requiring pressor support and his respiratory function declined. His intensive care unit stay was prolonged and complicated by acute renal failure requiring dialysis and disseminated intravascular coagulation (DIC). When finally extubated, he exhibited marked hypophonia and bradykinesia. One year later, he demonstrates severe residual parkinsonism which has been unresponsive to levodopa (450 mg/day). Examination reveals frequent yawning, severe hypophonia, hypomimia, asymmetric rigidity and bradykinesia, freezing of gait, and postural instability (Video S1). He has a positive grasp reflex with an impaired Luria test.

Computed tomography (CT) brain scan post-extubation demonstrated edema in the globus pallidus bilaterally and deep cerebellar nuclei containing small hemorrhagic foci (Fig. 1A,B). Magnetic resonance imaging (MRI) brain scan 3 weeks later confirmed these focal findings (Fig. 1C,D). Repeat MRI brain scan 3 weeks subsequently showed resolution of edema with tissue loss consisting of atrophy in the globus pallidus and severe tissue loss in the dentate nuclei. Susceptibility-weighted imaging in these nuclei confirmed iron deposition from hemorrhage in these structures (Fig. 1E-J). Diffuse white matter ischemic/hemorrhagic changes were not present. These imaging findings support a devastating but focal process affecting the globus pallidus and dentate nuclei

with hemorrhage (particularly prominent in the dentate nuclei) and gliosis.

Isolated basal ganglia involvement without diffuse cortical involvement is rare in hypoxic-ischemic injury but occurs more frequently due to respiratory or hypovolemic-shock mechanisms.⁹ Another reported COVID-19 case with similar pallidal imaging changes presented with refractory hypoxemia requiring intubation and developed shock, DIC, and acute renal failure.¹⁰ MRI revealed symmetric T2 prolongation in the bilateral globus pallidus as well as the hippocampi and substantia nigra but no dentate abnormalities. The authors concluded that hypoxic-ischemic injury was the likely etiology but no parkinsonism was reported.

Disseminated cerebral microhemorrhages, distinct from the changes evident in our patient, are well-described sequelae of critical illness.¹¹ However, microhemorrhages also result from SARS-CoV-2-induced endotheliitis and have been observed in the basal ganglia (but not dentate nuclei) in post-mortem COVID-19 studies.¹² A recent neuropathological study of 41 patients who died from COVID-19 found hypoxic/ischemic changes in all brains, many of which were hemorrhagic.¹³ These findings were focal in 22% of the cases. In addition, microglial nodules and neuronophagia were seen in multiple areas, including the deep cerebellar nuclei. No evidence of direct invasion by SARS-CoV-2 was seen. Although the radiological and clinical features in our case could be attributed to hypoxia alone, it is possible that other mechanisms including cytokine-related neuroinflammation, microglial activation, endothelial dysfunction, and megakaryocyte-mediated hemodynamic changes¹⁴ resulting from systemic SARS-CoV-2 infection may have contributed synergistically to our patient's presentation. Indeed, the hemorrhagic dentate changes, which are distinctly unusual for isolated hypoxia,⁹ suggest the possibility of additional contributing pathophysiological mechanisms.

This case highlights an important alternative, albeit poorly understood, cause of COVID-19-associated parkinsonism, distinct from unmasking of pre-existing Parkinson's disease or a form of yet unproven post-infectious parkinsonism. Given the degree of respiratory compromise and "silent hypoxemia" which may accompany COVID-19, as well as potential virus-specific endothelial mechanisms, this may represent an equally, if not more important cause of parkinsonism that requires further careful documentation and study. ●

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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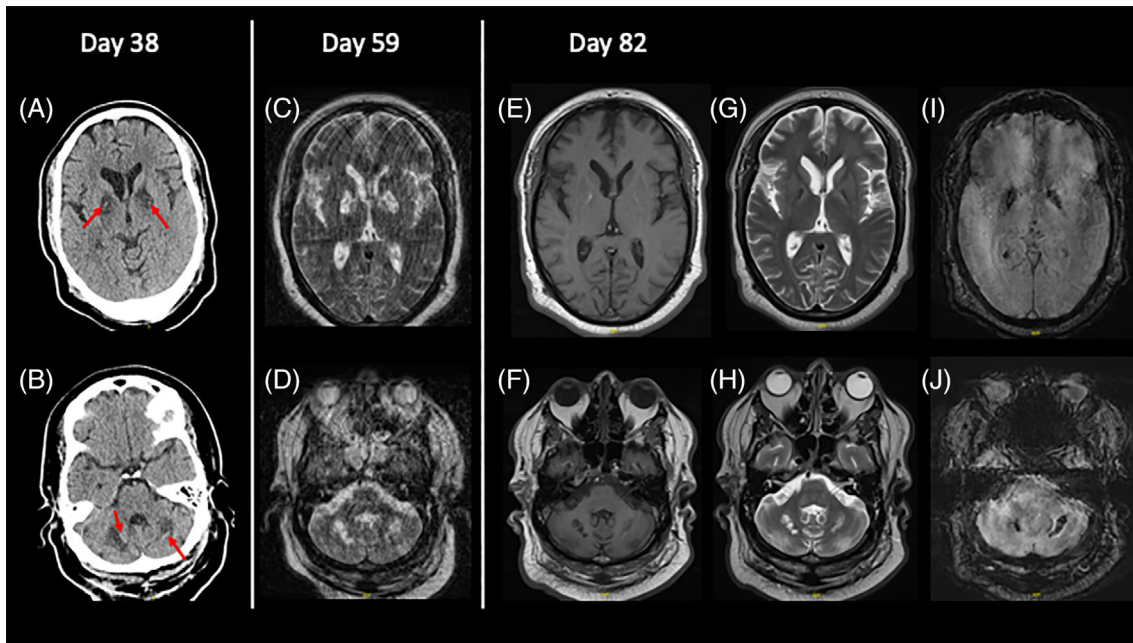


FIG. 1. (A,B) Computed tomography brain scan on day 31 of admission demonstrating edema and small hemorrhages (red arrows) in the globus pallidus and dentate nuclei. (C,D) T2 axial magnetic resonance imaging (MRI) sequence on day 59 of admission showing marked hyperintensity of globus pallidus and dentate nuclei. (E,F) T1 axial MRI sequence on day 82 of admission demonstrating atrophy of the globus pallidus and tissue loss within the dentate nuclei (right > left). (G,H) T2 axial MRI on day 82 of admission showing subtle hyperintensity of globus pallidus consistent with gliosis and severe tissue loss in the dentate nuclei (right > left). (I,J) Susceptibility-weighted imaging on day 82 of admission revealing susceptibility artefact within globus pallidus and dentate nuclei (left > right) confirming iron deposition from hemorrhage. [Color figure can be viewed at wileyonlinelibrary.com]

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Supporting Data

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