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Short Communication

A Neuroimmunological Axis between systemic autoimmunity and Parkinson's disease following long-COVID: A case series

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Highlights

- Long COVID may precipitate de novo autoimmune and inflammatory diseases.
- Immune dysregulation may link Long COVID, autoimmunity, and neurodegeneration.
- Central dopaminergic pathways may be vulnerable to post-viral immune mechanisms.
- Interplay between viral sequelae and immune pathways warrants further investigation.

Abstract

Background

Long COVID, a multisystemic syndrome following SARS-CoV-2 infection characterized by persistent immune dysregulation, systemic inflammation, and neuroimmune dysfunction, is a significant area of investigation in the neurological sciences. The hypothesis that this pathophysiological state can trigger de novo autoimmune diseases and potentially accelerate underlying neurodegenerative processes is gaining traction. This case series aims to illuminate the potential neuroimmunological link between these conditions by presenting the patients who developed de novo Crohn's disease (CD) and ankylosing spondylitis (AS) following Long COVID and were subsequently diagnosed with post-COVID Parkinson's Disease.

Case presentations

The first case is a 50-year-old female who developed de novo Crohn's disease (CD) six months after COVID-19 pneumonia, managed with with the TNF-α inhibitor. Eighteen months later, she presented with parkinsonian motor deficits. The post-COVID PD diagnosis was supported by susceptibility-weighted MRI showing loss of nigrosome-1 and DAT-SPECT revealing a presynaptic dopaminergic deficit. The second case is a 48-year-old female who was diagnosed with de novo ankylosing spondylitis (AS) eight months post-COVID, treated with adalimumab. Twenty-six months later, she developed progressive bradykinesia and rigidity. Neuroimaging confirmed post-COVID PD with corresponding loss of nigrosome-1 and a presynaptic dopaminergic deficit on DAT-SPECT. In both genetically negative cases, dopaminergic therapy led to substantial motor improvement, with UPDRS-III scores decreasing from 8 to 3 and 14 to 4, respectively.

Conclusion

This case series proposes a pathogenic cascade wherein SARS-CoV-2 infection acts as an environmental trigger, initiating a Long COVID-associated immune dysregulation that first precipitates a systemic autoimmune disorder. We hypothesize that this sustained inflammatory milieu subsequently accelerates the dysfunction of the dopaminergic system in predisposed individuals, thereby unmasking the clinical phenotype of post-COVID PD. This novel association highlights a potential nexus between virally-induced autoimmunity and subsequent neurodegeneration, offering a new perspective in the field of neuroimmunology.

Introduction

The COVID-19 pandemic has brought to the forefront not only acute viral symptoms but also Long COVID syndrome, characterized by persistent immune dysfunction and multisystemic effects (Heo et al., 2024). Long COVID may predispose some individuals to the emergence of new-onset autoimmune and inflammatory diseases (Heo et al., 2024). These immune-mediated pathophysiological processes can trigger the development of de novo Crohn's disease (CD) or ankylosing spondylitis (AS) by affecting the gastrointestinal and musculoskeletal systems (Heo et al., 2024; Peng et al., 2023). Less commonly, they can lead to early dysfunction of the central dopaminergic system, leading to the clinical manifestation of Parkinson's disease (PD) which have

described new-onset Parkinson's disease following SARS-CoV-2 infection, supporting the possibility of post-COVID PD (Calculli et al., 2023; Sulzer et al., 2020). In this case report, we present cases of de novo tremor-dominant and akinetic-bradykinetic forms of post-COVID PD, which were first described in patients diagnosed with de novo CD and AS after contracting COVID-19.

A 50-year-old female patient with no prior history of chronic illness or regular medication use presented to the emergency department with complaints of fever, sore throat, and widespread arthralgia and myalgia. A nasopharyngeal swab tested positive for SARS-CoV-2 via RT-PCR. Chest computed tomography (CT) revealed bilateral, peripheral ground-glass opacities, consistent with moderate COVID-19 pneumonia. Laboratory findings showed significantly elevated inflammatory markers, including ferritin (528.36 μg/L), D-dimer (0.86 mg/L), and C-reactive protein (CRP) (107.20 mg/L). Hemoglobin was 13.7 g/dL, platelet count 455×10^9/L, and serum albumin 3.1 g/dL. The patient was treated with ceftriaxone (1 g IV daily) and azithromycin (250 mg PO daily) for five days, and moderate clinical improvement was observed. Approximately six months after discharge, the patient presented to the gastroenterology outpatient clinic with progressively worsening nausea, cramping abdominal pain, and non-bloody, non-mucoid diarrhea. She reported an unintentional weight loss of 10 kg over the previous four weeks due to appetite loss and abdominal spasms. Physical examination revealed diffuse tenderness in the periumbilical region and a rectal fissure. Laboratory tests indicated iron deficiency anemia (Hb: 8.7 g/dL), thrombocytosis (platelets: 580×10^9/L), and elevated inflammatory markers (ESR: 108 mm/h). The stool occult blood test was positive. Urine and stool cultures were negative for infectious agents, and a repeat RT-PCR test for SARS-CoV-2 was also negative. Autoimmune markers, including HLA—B27, ANA, and anti-SSA/SSB, were also negative. Pelvic MRI with STIR sequences showed a ~ 5 mm enhancing inflammatory lesion at the level of the anal verge and increased signal intensity in the left subcutaneous adipose tissue. Liver and biliary imaging were unremarkable. Small bowel MRI demonstrated a 3.5 cm segment of wall thickening, mild diffusion restriction, and focal luminal narrowing in the terminal ileum near the ileocecal valve (Fig. 1A). Based on clinical, laboratory, and imaging findings, a diagnosis of post-COVID de novo CD was established. The patient was started on infliximab (5 mg/kg IV every 8 weeks). A moderate improvement in abdominal symptoms and inflammatory markers was observed following the initiation of treatment. Approximately 18 months after the initial COVID-19 diagnosis, the patient presented to the neurology clinic with complaints of resting tremor in the left hand and mild bradykinesia. The patient underwent a structured neurological assessment and a systematic history taking, focusing on both motor and non-motor Parkinsonian features. Family history for parkinsonism and early neurodegenerative disease was recorded; neither patient reported a first-degree relative with a known movement disorder. Non-motor domains were screened using structured clinical interviews for REM sleep behavior disorder (RBD) symptoms, autonomic dysfunction, mood and anxiety symptoms, and subjective cognitive complaints. No objective evidence of neurocognitive impairment was found; however, the patient exhibited a marked increase in RBD manifestations and anxiety symptoms over the past year. Genetic testing for a targeted parkinsonism next-generation sequencing panel was performed and included at a minimum SNCA, LRRK2, PRKN (PARK2), PINK1, PARK7/DJ-1, VPS35, and GBA, and no pathogenic or likely-pathogenic variants were detected. Neurological examination revealed left-dominant, low-amplitude resting tremor and prominent spasticity in the left upper extremity. Motor severity was quantified with the Unified Parkinson's Disease Rating Scale (UPDRS) Part III score and a Modified Hoehn and Yahr Stage (mH&Y). At initial presentation, the UPDRS-III score was

8, and the mH&Y was 1.5. Metabolic, toxic, and infectious causes of parkinsonism were ruled out with comprehensive laboratory panels. Susceptibility-weighted imaging (SWI) sequence of a 3 Tesla high-field power brain MRI performed for differential diagnosis revealed loss of the typical hyperintensity of nigrosome-1 within the substantia nigra pars compacta (Fig. 2A). Dopamine transporter imaging (DAT-SPECT) showed marked asymmetric reduction in dopamine transporter binding in the right putamen, consistent with presynaptic dopaminergic degeneration (Fig. 3A). Considering the clinical presentation, supportive neuroimaging findings, the exclusion of alternative etiologies, and the temporal proximity to SARS-CoV-2 infection, the patient was diagnosed with tremor-dominant PD, potentially associated with Long COVID. The patient was initiated on pramipexole (1.5 mg/day) and rasagiline (1 mg/day). At scheduled follow-up visits, after initiation of dopaminergic therapy, the 2-week follow-up showed a marked improvement: the UPDRS-III score decreased to 3, and the mH&Y stage improved to 1, reflecting a clear acute symptomatic response. At the 3-month visit, motor scores and mH&Y stage remained sustained and comparable to those at the 2-week assessment, consistent with a maintained clinical benefit.

Shortly after treatment initiation, motor symptoms improved significantly; UPDRS motor score decreased to 3, and Hoehn and Yahr Stage improved to 1.
A 48-year-old woman with no chronic disease or regular medication presented to the emergency department with complaints of headache, sudden-onset loss of taste and smell, nausea, recurrent vomiting, and watery diarrhea lasting three days. She also complained of significant fatigue and occasional palpitations. A nasopharyngeal swab was positive for SARS-CoV-2 by RT-PCR. A chest CT scan revealed bilateral, peripherally located ground-glass opacities, consistent with moderate COVID-19 pneumonia. Laboratory tests revealed moderately elevated inflammatory markers, including ferritin (418 μg/L), D-dimer (0.64 mg/L), and CRP (20.5 mg/L). Hemoglobin was 11.7 g/dL, platelet count 405×10^9/L, and serum albumin 2.8 g/dL. The patient received fluid support, antiemetic therapy, and combined antibiotics (ceftriaxone (1 g/ IV/day + doxycycline (100 mg PO/day) for 5 days and was discharged after clinical findings improved. Approximately eight months after her COVID-19 diagnosis, the patient presented with worsening low back pain radiating to both hips, stiffness aggravated by rest, and morning immobility, all of which had progressively worsened over the previous three months. A pelvic MRI revealed an ~8 mm intramedullary lesion at the left acetabular level, which was hyperintense on STIR and enhanced with contrast. MRI of the sacroiliac joints showed subchondral bone marrow edema in both superior and inferior aspects of the bilateral sacroiliac joints, as well as soft tissue edema in the posterior joint regions consistent with enthesopathy (Fig. 1B). Based on clinical symptoms and radiologically confirmed sacroiliitis, a diagnosis of de novo AS was made in accordance with the Modified New York Criteria. The patient was started on adalimumab (40 mg SC every two weeks). Following the therapy and the addition of physical therapy, moderate clinical improvement in rheumatologic symptoms was achieved. Approximately 26 months after the initial COVID-19 diagnosis, the patient presented to the neurology outpatient clinic; her most prominent complaints were slowed movements, decreased arm swing, and rigidity, with symptoms more severe on the right side. Examination revealed marked bradykinesia in the right upper and lower extremities, decreased right arm swing during walking, and cogwheel rigidity in the right upper extremity; resting tremor was minimal. The patient underwent a structured neurological assessment, and the focused history and family history for parkinsonism were negative. Non-motor screening was performed and revealed no objective evidence of neurocognitive impairment. Notably, the patient reported stress urinary incontinence,

which was evaluated and judged to be independent of primary urological pathology after COVID-19 period. Genetic testing was performed using a targeted PD's next-generation sequencing panel, and no pathogenic or likely pathogenic variants were identified. Motor assessment revealed a UPDRS-III score of 14 and a mH&Y stage of 2. Metabolic, toxic, infectious, and genetic causes of parkinsonism were excluded through comprehensive laboratory and genetic panels. A 3-Tesla SWI MRI performed for differential diagnosis revealed marked hypointensity and loss of nigrosome-1 signal in the left substantia nigra pars compacta (Fig. 2B). There was also a decreased signal in the dorsolateral portion of the substantia nigra consistent with increased iron deposition. DAT-SPECT imaging revealed a marked loss of dopamine transporter binding in the left posterior putamen. These findings indicate presynaptic dopaminergic degeneration, consistent with an akinetic-bradykinetic phenotype (Fig. 3B). Based on the clinical findings, neuroimaging findings, exclusion of alternative etiologies, and the proximity in time to SARS-CoV-2 infection, the patient was diagnosed with akinetic-bradykinetic post-COVID PD. Treatment was initiated with carbidopa/levodopa 100/25 mg three times daily (total levodopa 300 mg/day) and rasagiline 1 mg/day. After initiation of dopaminergic therapy, the patient demonstrated a marked clinical improvement. At the 2-week follow-up, the MDS-UPDRS-III score decreased to 4, and the mH&Y stage improved to 1.5. At the 3-month visit, motor scores and the mH&Y stage remained comparable to those at the 2-week assessment, consistent with sustained symptomatic benefit.

Section snippets

Discussion

This report describes two patients in whom the emergence of distinct systemic autoimmune diseases and subsequent PD temporally followed SARS-CoV-2 infection. Complex cases involving combined autoinflammatory and immune-neurodegenerative manifestations after SARS-CoV-2 infection remain exceedingly rare, and this concurs with the potential complexity and inter-individual variability of immune-neurodegenerative interactions in the context of Long COVID.

It is now well recognized that SARS-CoV-2 can …

Statement of informed consent

Informed consent was obtained from participants for inclusion in this case series, including permission for publication of MRI sequences. …

CRediT authorship contribution statement

Esra Demir Unal: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. …

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Declaration of competing interest

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