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Case report

Parkinsonism: An emerging post COVID sequelae

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ABSTRACT

Parkinsonism has a complex and multifactorial aetiology and the role of post viral infection parkinsonism has been documented. The recent pandemic has made it clear that COVID-19 causes respiratory disease and affects multiple organs, which includes the central nervous system. Here we report three cases of post COVID parkinsonism occurring in older adults, age 60 years and above, and their response to levodopa-carbidopa.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder affecting 1% of the population above 60 years of age with an annual incidence of 15 per 100,000 population [1]. A complex and multifactorial aetiology resulting from environmental contributions is suspected of playing a role in PD's pathogenesis. Genome-wide association studies have identified genetic links as risk factors for the development of PD [2,3]. However, sporadic occurrences suggest an interaction between other factors, which remain enigmatic. Literature suggests an association between viruses such as influenza A, Epstein-Barr virus, hepatitis C virus, varicella-zoster, West Nile virus and Japanese encephalitis virus [4]. We report three cases of patients with COVID-19 developing parkinsonism and responding to levodopa.

Case 1

A 72-year-old male patient with no past comorbidities presented with fever, chills, cough and breathlessness of four days. He was diagnosed with COVID-19 by a real-time reverse transcription PCR assay and treated with intravenous dexamethasone, intravenous remdesivir and heparin for five days. The patient developed acute kidney injury (AKI) and was shifted to our facility.

At the time of admission, his temperature was 96.5 degrees F, pulse: 91/minute, blood pressure was 130/70 mm Hg, SpO2 was 98% on room air. He had left upper limb swelling with redness due to cellulitis. His total leukocyte count was 17,900/microliter (4000 - 11,000/microliter) with 85.9% neutrophils and 7.5% lymphocytes, serum urea was 122 mg/dL (15–43 mg/dL), creatinine 2.4 m/dL (0.62–1.1 mg/dL), aspartate aminotransferase 130 U/L (0 – 35 U/L), alanine aminotransferase 83 IU (0 – 35 U/L), erythrocyte sedimentation rate 52 mm in 1st hour, C-reactive protein > 90 mg/L (0–10 mg/L), serum ferritin 704 microgram/L (18 – 464 microgram/L), D-dimer 4264 ng/mL (< 500 ng/mL), serum lactate dehydrogenase 322 Unit/L (120 – 246 Unit/L) and random blood sugar 366 mg/dL. Venous doppler of the left upper limb revealed superficial thrombophlebitis of the basilic vein. He was treated with intravenous antibiotics, methylprednisolone, heparin and subcutaneous insulin.

On day 5 of hospitalisation, his son noticed that he was having freezing episodes in the washroom, it was difficult to mobilise him, and he also had three episodes of falls. On examination, he was found to have orthostatic hypotension (supine BP 130/70 mmHg and 3 min standing BP 80/60 mmHg), loss of smell, cog-wheel rigidity, postural instability and bradykinesia. He was advised bed rest till complete recovery from his acute illness, and treatment was continued. His total leukocyte counts normalised (8820/microliter), inflammatory markers decreased (CRP: 18.2 mg/L, D-Dimer 777.9 ng/mL), but his rigidity, postural instability and bradykinesia persisted despite resolution of the acute illness.

A diagnosis of parkinsonism was considered based on the clinical features. The postural hypotension was managed with increased fluid and salt intake and compression stockings, and started on levodopa 110 mg, half tablet four times a day. With these measures, the patient's symptoms improved. He had no falls, the rigidity subsided, and gait speed increased. On followed up after four months he reported complete resolution of symptoms and performed his activities of daily living independently.

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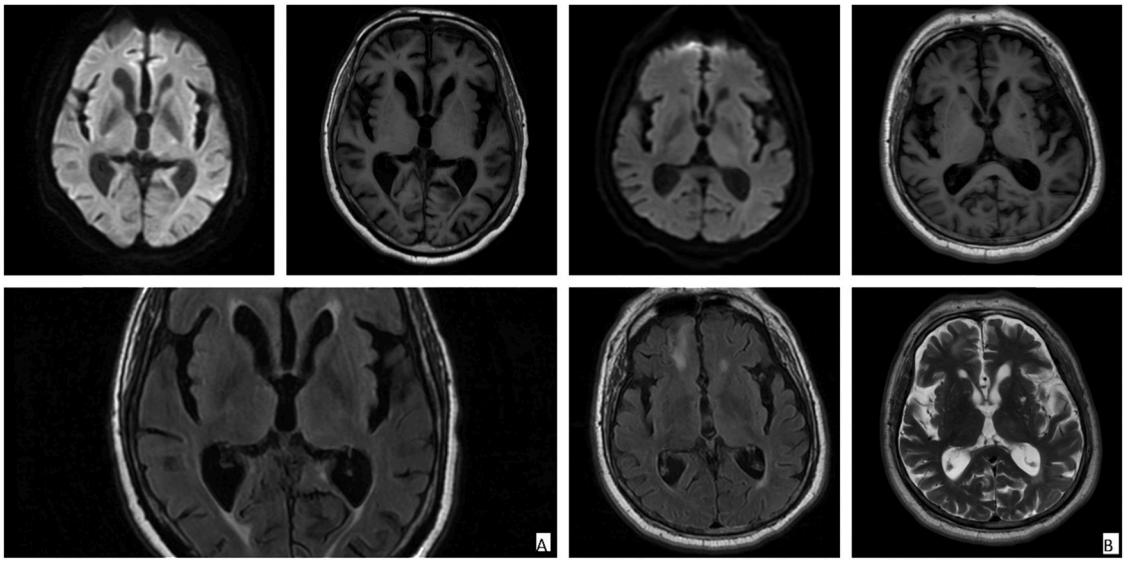

Fig. 1. Magnetic resonance imaging (MRI) of two patients with DWI, T1, T2, FLAIR sequence, reveal age related changes including brain atrophy, small vessel changes and white matter hyperintensities.

Case 2

A 66-year-old male patient presented to us with cough, hoarseness of voice for two weeks and one episode of a generalised tonic-clonic seizure. His medical history was remarkable for diabetes mellitus, hypertension and seizure disorder controlled with medications.

On examination, his pulse was 96/minute, and his blood pressure was 90/70 mmHg, respiratory rate of 28/minute and SpO2 of 90% on room air. Respiratory examination revealed bilateral basal crepitations. The RT-PCR from nasopharyngeal swab was positive for SARS-CoV-2. He was resuscitated with oxygen via face mask, intravenous normal saline in the emergency room and shifted to the intensive care unit.

His haemoglobin was 13.1 gm/dL (13–17 gm/dL), total leukocyte count was 7820/microliter, urea 46 mg/dL, creatinine 0.6 mg/dL, C-reactive protein > 90 mg/L, D-dimer 1117.6 ng/mL, lactate dehydrogenase 313 U/L, serum ferritin 343 microgram/L. He was started on intravenous dexamethasone and anti-coagulation.

After one week, there was an improvement in his vitals and laboratory parameters, but clinically there was no improvement. The patient remained immobile and mute. Examination revealed rigidity in his right upper and lower limbs with severe bradykinesia. His brain magnetic resonance imaging showed (Fig. 1(A)) gliosis in bilateral temporal lobes, periventricular punctate white matter ischemic changes in bilateral frontal and parietal lobes and age-related cerebral and cerebellar atrophy. Cerebrospinal fluid analysis revealed a cell count of 2/cubic millimetre, glucose 81 mg/dL, protein 40 mg/dL, LDH 88 U/L (120 – 246 U/L), adenosine deaminase 2.05 U/L (0–5 U/L), negative for acid-fast bacilli, India ink negative for Cryptococcus neoformans, negative for malignant cytology.

He was given a trial of levodopa-carbidopa, following which his mobility and speech improved. After one month, with optimisation of levodopa and physical rehabilitation the patient was mobile and completely independent for his activities of daily living.

Case 3

A 74-year-old male with a history of COVID-19 eight weeks before admission presented to us with decreased mobility which he developed during the previous hospitalisation. During his previous hospitalisation his haemoglobin was 14.2 gm/dL, total leukocyte count 12,970/microliters, urea 195 mg/dL, creatinine 6.9 mg/dL, C-reactive protein 54.4 mg/L. His chest computer tomography (CT) revealed central and peripheral ground-glass opacities in bilateral lung fields, predominantly in the lower lobes with consolidation of the left lower lobe, with severity score of 13/25. His acute respiratory illness and acute kidney injury resolved, but he continued to remain immobile.

On examination, he was afebrile, neurological examination was significant for rigidity, postural instability and motor slowing. His investigations revealed a haemoglobin of 12.5 gm/dL, a total leukocyte count of 10,050/microliter, a C-reactive protein of 8.6 mg/L. His MRI brain (Fig. 1(B)) revealed ischemic changes in periventricular white matter. His cerebrospinal fluid analysis showed two cells/cubic millimetre, 100% lymphocytes, glucose 120 mg/dL, protein 33 mg/dL, LDH 64 U/L, ADA 0.0 U/L, gram-stain and culture revealed no growth.

Because of persistent parkinsonism, he was started on levodopa-carbidopa and physiotherapy was continued. This resulted in decreasing rigidity, improved mobility, speech and swallowing. At six months follow-up, the patient could walk independently, with a timed-up and go (TUG) score of 18 s

Discussion

Parkinsonian symptoms refer to PD-like clinical features, including progressive rigidity, bradykinesia, postural instability, oculomotor abnormalities and cognitive impairment, not accounting for PD diagnosis. The association of bacterial and viral infections with parkinsonism has been indicated in recent studies, though the causation is yet to be established. The hypothesis implicating infectious origin in PD comes from observing parkinsonism in patients infected with influenza virus developing encephalitis lethargica and postencephalitic Parkinsonism (PEP) [5]. The events were temporally coincidental and PEP was clinically and pathologically distinct from idiopathic PD. Patients with PEP did not exhibit cognitive disturbances, including apasia and apraxia, seen in idiopathic PD. Clinical research suggests that, between 1925 and 1938, influenza A played a role in almost 50% of all diagnosed cases of Parkinsonism [6].

The present pandemic has made it clear that COVID-19 causes respiratory disease and affects multiple organs. The central nervous system (CNS) involvement is of note, and is independent of the severity of respiratory disease. COVID-19 binds to angiotensin-converting enzyme 2 (ACE2) receptors to access human cells, making cells expressing ACE2 targets for infection. It has been reported that glial cells and neurons in the brain express ACE receptors, making them potential targets [7,8].

Table 1
Post COVID-19 Parkinsonism.

Age	Days to parkinsonism after initial COVID symptoms	Clinical features	Prodromal symptoms	Response to levodopa-carbidopa
72 year	14 days	Freezing Recurrent falls Orthostatic hypotension Anosmia Cog-wheel rigidity bradykinesia	None	Yes
66 year	2 weeks	Akinetic mutism Rigidity	None	Yes
74 year	3 weeks	Immobile Postural instability Rigidity bradykinesia	None	Yes

Neurological Manifestation of COVID-19

The most common neurological manifestation in COVID-19 patients was headache. The mean prevalence was 8% in a systematic review [9], followed by dizziness (7–9.4%) and confusion [10]. Other manifestations were acute ischemic stroke, cerebral venous sinus thrombosis, cerebral haemorrhage, meningitis/encephalitis, and Guillain-Barre syndrome and acute necrotising haemorrhagic encephalopathy [11]. Symptoms involving the cranial nerves, such as hyposmia, hypogeusia, hypopsia and neuralgia, were reported in 8.9% of subjects [12]. Impairment of smell and taste are identified as an early manifestation in the first five days of illness. The prevalence of neurological manifestations was underestimated in the early stages of the outbreak.

Evidence of neurotropism

Since the viral structure and receptor-binding domain of SARS-CoV and COVID-19 are similar, the evidence found for SARS-CoV may apply to COVID-19. CSF samples have been tested positive [13], the virus has also been isolated from brain specimen supporting the neurovirulence of SARS-CoV. Brain tissue has indicated neuronal necrosis, and glial cell hyperplasia [14], viral particles and genomic sequence were detected in neurons from cases of SARS autopsies. The virus enters the brain through the olfactory bulb and spreads trans-neuronally to related zones in the brain. One case of meningitis/encephalitis was reported where COVID-19 RNA was detected in the CSF specimen [15], providing evidence of neuro-invasiveness of COVID-19.

A possible explanation of parkinsonism in COVID-19

The two main routes for viruses to enter the CNS are hematogenous and neuronal retrograde dissemination. In addition to direct injury of the brain, the possible pathophysiology of post-infectious parkinsonism includes neuroinflammation, potential role of alpha-synuclein [4], structural and functional basal ganglia damage involving substantia nigra pars compacta, hypoxic brain injury in the context of encephalopathy, the unmasking of underlying pre-symptomatic Parkinson's disease [16].

To date, few COVID-19 related cases of parkinsonism have been reported [17–19]. The patients' age ranged from 35 to 58 years, with the COVID-19 severity being mild to severe requiring intensive care unit (ICU) admission. The duration between the first symptom of COVID-19 to features of parkinsonism ranged from 5 days to 32 days, with tremors, rigidity and bradykinesia being present in all. Our patients (Table 1) were older adults with two patients age more than 70 years. The duration between the first symptom of COVID-19 to features of parkinsonism ranged from 14 days to 3 weeks, and symptoms included tremors, rigidity, bradykinesia and akinetic mutism. All three patients showed response to levodopa-carbidopa. None of the patients had any history suggestive of parkinsonism or taking medications, leading to secondary Parkinsons before developing a COVID-19 infection. Our experience, along with observations by others involved with patient care [20], indicates a possible link between symptoms of parkinsonism and COVID-19.

Conclusion

COVID-19 has been identified by its prominent fever, cough, and dyspnea symptoms, but it is essential to highlight the neurological manifestations, as these manifestations might be overlooked. In the three cases we have described, the patients did not have any features of parkinsonism before the onset of COVID-19, and all three of them responded to levodopa. This suggests that parkinsonism could be one among the post-COVID sequelae, and physicians need to be aware of this entity as timely initiation of therapy leads to improvement in the patient's condition and quality of life.

Ethical approval

Not applicable

Consent

Written informed consent was obtained from the patients for publication of this case series.

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CRediT authorship contribution statement

Abhijith Rajaram Rao: Writing, Data analysis, Editing. **Shaik Mohammed Hidayathullah:** Data collection, Writing. **Karan Hegde:** Writing, Editing. **Prabha Adhikari:** Conceptualization, Data analysis, writing.

Conflict of interest

All authors declare no conflict of interest.

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