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Case Report

Possible Parkinsonism Following COVID-19 Infection

Sam Kara[1]*, Reza S Roghani[2], Pamela Youssef[1] and Kester Nedd[1]

[1]Department of Neurology, Larkin Community Hospital Palm Springs Campus, Miami, Florida, USA

[2]Department of Physical Medicine and Rehabilitation, Larkin Community Hospital South Campus, Miami, Florida, USA

***Corresponding Author:** Sam Kara, Department of Neurology, Larkin Community Hospital Palm Springs Campus, Miami, FL 33012, USA, samkara72@gmail.com.

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Abstract

Neurological complications, both acute and long- term, have been reported during the COVID-19 infection pandemic. Aside from idiopathic Parkinson's disease (PD), there are rare presentations of atypical parkinsonian syndromes. Infection, as an etiology, leading to PD or parkinsonism is rare. However, this hypothesis gained more traction as a result of the few cases reported during the COVID-19 pandemic. To date, less than a handful of reports describe parkinsonian type disease complications following COVID-19 infection. These cases, including this report, are important to establish the exact etiology and demographics (sex, age, and race) for this devastating COVID-19 sequelae. The COVID-19 virus was found to infiltrate and impact the central nervous system (CNS) through hematogenous and lymphatic routes, and through the cribriform plate via the olfactory bulb. These cases help to delineate the risk factors, improve our understanding of the duration and course of disease, treatment options, and solidify our knowledge of comorbidities affecting the presentation. We present a case of acute parkinsonism post-COVID-19 infection in an immunocompetent female. A brain Magnetic resonance imaging (MRI) revealed lesions in both the white matter and Globus palladium changes. All lesions had homogeneous contrast enhancement without any sign of hemorrhage, and affecting mostly the supratentorial punctiform and pontine areas. Patient symptoms improved on a trial of levodopa-carbidopa.

Keywords: Parkinson's Disease; Parkinsonism; COVID-19; Tremor; Levodopa

Introduction

COVID-19 infection has claimed, so far, over 900,000 lives in the USA alone. A range of associated neurological complications, including cerebral thrombosis [1,2] and demyelinating diseases have been described [3-5], as well as an autoimmune etiology post-infection has been proposed. Few cases of post COVID-19 have been reported [6-8]. We report a parkinsonian syndrome after COVID-19 infection, in an otherwise healthy 57-year-old female patient. Parkinsonism is defined by any condition that causes a combination of the movement abnormalities seen in Parkinson's disease such as slow movement, tremor, impaired speech, or muscle stiffness. A parkinsonian syndrome is associated with significant morbidity and mortality which necessitates increased clinical vigilance, especially considering a possible link during the pandemic [9].

Not every patient with parkinsonism has Parkinson's disease thus differentiating the two categories is important. The atypical parkinsonian syndromes are classified as synucleinopathies [10] and tauopathies [11]. These disorders are characterized by the abnormal deposition of the proteins α-synuclein and tau in the brain, and the site of deposition correlates with the clinical features [12]. In Lewy body dementia (LBD), the synuclein is deposited in neocortical neurons which correlates with dementia and parkinsonism, while in Multi-System Atrophy (MSA), synuclein

protein is deposited in the cerebellum (oligodendrocytes) and causes autonomic dysfunction and cerebellar ataxia or parkinsonism. Progressive supranuclear palsy (PSP) commonly presents with vertical gaze palsy as well as early onset postural instability with falls. Typically, Corticobasal degeneration (CBD) manifests as markedly asymmetrical parkinsonism with apraxia or cortical sensory disturbance. PD is caused mainly by the degeneration of nerve cells in the brain, while parkinsonisms are caused by many etiologies including 1) Medications- used in the treatment of major psychiatric disorders and nausea, 2) Repeated head trauma- common in boxing or football, 3) Neurodegenerative disorders- such as MSA, LBD, and PSP, 4) Toxins- including carbon monoxide, cyanide, and organic solvents, 5) Certain brain lesions- such as tumors, or fluid buildup, 6) Metabolic disorders- including chronic liver failure or Wilson's disease, 7) Viral– Spanish flu. Here, we present a patient with acute parkinsonism after COVID-19 infection.

Case Presentation

We present a previously healthy 57-years-old female, with a history of hypertension, chronic headaches, and no history of prodromal symptoms of PD. In October 2020, she acquired an asymptomatic COVID-19 infection confirmed by polymerase chain reaction (PCR) and denied a history of cough, shortness of breath, abnormal body movement, or exposure to carbon monoxide or other toxins. Shortly after infection (February, 2021) the patient's chronic headaches had increased in frequency and she developed associated neck pain and stiffness, fluctuating hypertension, less responsive to antihypertensives. In early July 2021, her chronic symptoms continued to deteriorate, and she developed a range of new-onset, slowly progressing symptoms including weakness, fatigue, blurry vision, loss of appetite, weight loss, and a progressive gait disturbance. The patient also reported challenges in her ability to perform daily tasks. For example, she was unable to stand for prolonged periods without dizziness and fatigue and could not perform her data-entry clerk job due to changes in her writing skills.

The patient's gait and writing changes triggered the patient to visit our Miami hospital in December 2021, after a referral from her primary care. On presentation, the patient's vitals were within normal limits except for her blood pressure which fluctuated between 200/100 mmHg and 140/90 mmHg within a ten-minute interval. No orthostatic hypotension changes were witnessed. On a physical exam, there was a noticeable impairment in her ability to fixate on a visual target While she did not present with micro-Square-Wave Jerks she did demonstrate slow saccades most prominent in the horizontal gaze and demonstrated oculomotor apraxia (overshooting or undershooting when tracking visual targets). These findings were replicated on head-turning test, along with hypomimia (facial masking), difficulty whistling (facial-oral apraxia), and decreased eye blink rate. No dysarthria, speech, or vocal tremor were observed. On testing of both head-turning and cervical range-of-motion, the patient was unable to fully turn her head to the right (associated feeling of tightness and rigidity) and revealed bilateral neck stiffness. Motor testing revealed hypertonicity with ratchet-like jerkiness on passive flexion and extension of her upper extremities and passive rotation of her wrists. Furthermore, the patient had bilateral, low amplitude hand tremors at rest. No sensory disturbances were appreciated on the physical exam. The patient had a positive 'jaw-jerk' reflex (contraction of her jaw on tapping of her chin) as well as positive frontal release signs (eye blink with each tap to the forehead and a contraction of the mentalis by muscle of the chin on stimulation of the thenar eminence). On gait examination, she demonstrated a slightly forward stooped, slow, cautious gait with absent arm swing, along with slow gait pivot and decreased step length throughout. She was treated with multiple courses of steroids with no benefit. Lumbar puncture and cerebrospinal fluid analysis showed no acute changes. Brain MRI without contrast FLAIR sequence revealed diffuse, punctate bilateral, asymmetric lesions throughout the cerebral cortex, subcortical gray matter and brainstem, with a predilection for the pons with a lesion measuring 2.2 cm, without mass effect. Patient age, illness course, laboratory findings, as well as the clinical exam and radiological findings are consistent with motor parkinsonism after COVID-infection.

Laboratory workup included a normal serology, blood analysis and normal CSF analysis and microbiology (Table 1). The Brain MRI lacking evidence of encephalitis and a clinical picture without altered mental status or encephalitis/meningitis symptoms (not consistent with encephalitis) further demonstrates a non-cerebral etiology. 3-Tesla MRI of gray matter was unremarkable, such findings contrasted with the patient's bilateral symptoms which could be due to microstructural changes in other brain pathways (Figure 1). Further radiological findings on white matter revealed

lesions with restricted diffusion (without any hemorrhage or enhancement) (Figure 1). All lesions had homogeneous contrast enhancement without any sign of hemorrhage. The thalamus, the striatum, and the posterior fossa were spared. The intracranial vessels were normal on time-of-flight and post contrast 3D T1-weighted black-blood images. Sinovenous thrombosis was observed. A second lumbar puncture was performed in December 2020. Which remained negative (exactly like table 1) and the patient RT-PCR for COVID-19 resulted negative. A follow-up MRI showed no extra or new lesions. A spinal cord MRI was without abnormalities. These findings are consistent with alternative diagnoses including Binswanger disease (subcortical leukoencephalopathy and subcortical arteriosclerotic encephalopathy) or Multiple sclerosis (MS). As U-fibers are spared and the lesions are not abutting the lateral ventricles, and clinically the presentation is not consistent with MS, it is less likely. Binswanger disease is also known as subcortical leukoencephalopathy. Though the patient fits in this age group, the disease typically manifests similarly to stroke or can present as mental deterioration and thus unlikely. The patient was started on carbidopa-levodopa 10mg-100mg three-times daily for two weeks. The patient reported minor improvement in tremor. The medication dose was increased to 25mg-100mg three-times daily. After a month, the patient reported impressive improvement in daily activity due to bilateral reduction of tremor, reduction of gait difficulties, and mood improvement.

Blood analysis	
Thyroid function (TSH, T4)	Negative
Parathyroid hormone	Negative
Vitamine B12	Negative
Folic acid	Negative
Serum copper	Negative
Ceruloplasmin	Negative
CSF analysis	
Glucose	75 mg/dL (40-80)
Total Protein	23.1 mg/dL (15-45)
White cell count	<5 cell/micro-L (0-10)
Oligoclonal bands	Negative
CSF Microbiology	
Enterovirus	Negative
Herpes simplex virus 1	Negative
Herpes simplex virus 2	Negative
Mycoplasma Pneumonia	Negative
Serology	
Tuberous sclerosis	8.1 g/dL (6.6-8.7)
HIV	Negative
HBV	Negative
HVC	Negative
Syphilis	Negative
Mycoplasma Pneumoniae	Negative

Table 1: Routine blood and CSF test measures.

Figure 1: Brain MRI of COVID-19-related lesions.

Fluid attenuation and inversion recovery (FLAIR) sequence of the white matter and showing hypersignal lesions involving the supratentorial punctiform (A), lesions involving pontine lesion (B), and the involve the corpus callosum with a mass effect (C).

Discussion

The Growing body of literature pointing to the development of common neurological complications associated with COVID-19 infections include headache, seizures, and stroke. Rare presentations have been also reported such as transverse myelitis [3] and Bell's palsy [13]. It has been shown that nervous system viruses can induce encephalopathy with parkinsonism as a secondary consequence. Some of these viruses which are known to induce parkinsonism include Coxsackie, St. Louis, West Nile, Japanese encephalitis B, and HIV viruses [14,15]. In parkinsonism associated with viral infections, pathology ranges from direct acute infection to post-infectious neuroinflammation leading to dopaminergic cell loss. The mechanism of the suspected degeneration of nigrostriatal dopaminergic nerve terminals remains unclear. One hypothesis considers the possibility that COVID-19 infection may precipitate, and unmask or accelerate neurodegenerative diseases. For example, the inflammation caused by the virus leads to microglial activation and contributes to protein aggregation and neurodegeneration. However, the short time interval between the acute infection and the parkinsonian symptoms makes this hypothesis unlikely. Others proposed the "multiple-hit hypothesis" in which both the toxic stress and inhibition of neuroprotective responses can lead to neuronal death. Furthermore, a susceptible genetic makeup may predispose patients to various clinical manifestations. The acute manifestations of COVID-19 encephalitis are related to the cytokine storm disrupting the blood-brain barrier and resulting in neurological manifestations. Clinical and laboratory pictures of our patient do not suggest she had encephalitis.

COVID-19 may unmask subclinical neurodegenerative disorders or worsen pre existing conditions, and may cause new onset disease. In the case presented, the patients lacked any symptoms of parkinsonism before the onset of COVID-19, and responded to levodopa. This suggests that parkinsonism could be secondary to COVID-19 infection, and physicians need to be vigilant of it as timely initiation of therapy improves patients' morbidity and quality of life. This patient responding to carbidopa-levodopa supports the diagnosis of parkinsonism.

Conclusion

In conclusion, we report a case of carbidopa-levodopa-responsive parkinsonism probably caused by direct COVID-19 infection, broadening the disease clinical spectrum.

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Conflict of Interest

Declare if any financial interest or any conflict of interest exists.

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