Post-acute COVID-19 Movement Disorders: Organic or Functional?

Jonathan T. Grossman[1]*, Andrew Hariraj[2], Sarra Fadali[3], Asia Filatov[1]

[1]Florida Atlantic University Charles E. Schmidt College of Medicine; Boca Raton, Florida, USA

[2]American University of Integrative Sciences; Cole Bay, Sint Maarten, USA

[3]Baruch College; New York, NY, USA

Corresponding Author*

Jonathan T. Grossman

Florida Atlantic University Charles E. Schmidt College of Medicine

Boca Raton, Florida, USA

Tel: (954) 673-5651

E-mail: jgdoneuro@gmail.com

Received: 16 June 2022, Manuscript No. NNR-22-66750; **Editor assigned:** 19 June 2022, PreQC No. NNR-22-66750 (PQ); **Reviewed:** 29 June 2022, QC No. NNR-22-66750 (Q); **Revised:** 5 July 2022, Manuscript No. NNR-22-66750; **Published:** 7 July 2022, **DOI.**10.37532/22.4.3.25-28

Abstract

As the list of neurological squeal of Severe Acute Respiratory Syndrome Coronavirus 2. (SARS-CoV-2) infection continues to expand; the number of recorded cases of post-acute Coronavirus Disease (COVID-19) movement disorders is on the rise. The possibility of a functional origin of these abnormal movements has been largely overlooked. Here we present a review of recent literature exploring para-and post-infectious movement disorders in COVID-19 patients.

Keywords: COVID-19 • Movement Disorders • CNS

Introduction and Background

Coronaviruses (CoV), so named for their crown or spike-like cell surface proteins, were first discovered in the 1960s and include 4 sub-groups: alpha, beta, gamma, and delta. Presently, there are a total of 7 coronaviruses known to affect humans: 229E, HKU1, NetherLand 63 (NL63), OC43, MERS-CoV, SARS-CoV-1, and SARS-CoV-2 [1]. The beta coronaviruses Middle East Respiratory Syndrome Coronavirus (MERS-CoV), SARS-CoV1, and SARS-CoV-2 can cause severe illness in humans. Neurological manifestations associated with CoV infection were described well prior to the 2020 SARS-CoV-2 pandemic. Historically, notable CoV outbreaks include the 2003 Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1) outbreak in Asia and 2015 MERS-CoV outbreak in Saudi Arabia. Documented neurological manifestations following infection with SARS-CoV1 and MERS-CoV include alterations in consciousness, headache, affective disorders, ataxia, seizures, generalized pain, and persistent anosmia [2,3]. Managing neurological disease in COVID-19 patients has proven exceedingly difficult. While hypoxia or ischemia-related Central Nervous System (CNS) damage has been proposed as a potential trigger, the presence of anti-neuronal antibodies in the serum and Cerebrospinal Fluid (CSF) of COVID-19 patients in combination with the absence of hypoxia induced CNS damage on postmortem studies suggests the existence of alternative mechanisms of injury.

Aside from hematogenous dissemination, the prevailing theory is that neurotropism results in direct damage to the peripheral or CNS with invasion mediated by Angiotensin-Converting Enzyme 2 (ACE-2) receptors on the surface of cells that comprise neuronal tissue. Support for this theory comes, in part, from the discovery that olfactory epithelium expresses concentrations of ACE-2 receptors like that found in lung tissue. This could suggest a means of direct entry into the brain/CNS. A recent study of COVID-19 patients with otherwise unexplained neurological symptoms revealed elevated levels of autoantibodies in CSF, suggesting that autoimmunity may play a role in neuronal damage [4]. A recent presentation at the American Academy of Neurology 2022 annual meeting titled "Cognitive Symptoms After Mild SARS-CoV-2 Infection Associated with Higher Levels of CSF Immune Activation and Immunovascular Markers" suggests that SARS-CoV-2 induced immune activation may persist well after the acute illness and, thus, could cause persistent neurological symptoms. Several possible autoantigens have been described including Heat Shock Protein (HSP)A5, HSP 90-beta (HSP90AB1), titin, Ryanodine Receptor 2 (RYR2) [5]. Another study stratifying COVID-19 patients found increased incidence of thrombotic or neurological complications in patients with autoantibodies compared to those without [6]. Still, some studies have found no evidence of CNS viral invasion [7,8]. While postmortem brain biopsies of COVID-19 patients have shown evidence of hypoxic injury, no histopathological changes or cytoplasmic staining could be ascribed to the virus [9]. Although the specific neurobiology underlying neuronal injury remains undetermined it is likely that an interplay of mechanisms, including both innate and adaptive immune responses, contribute to neuronal damage.

Review

So-called "long COVID" is a term used to describe new, recurrent, or persistent health problems experienced 4 or more weeks following infection [10]. While there is still much to learn about this phenomenon, it appears to follow both asymptomatic and symptomatic infection. Commonly reported neurological symptoms include tiredness, difficulty thinking or concentrating, "pins-and-needles" feeling, sleep problems, dizziness, mood changes, and changes in smell or taste. Proposed mechanisms include autoimmune conditions and multisystem inflammatory syndrome. Because some of these symptoms parallel those that can occur after any hospitalization, it is often difficult to discern their cause. Neurological issues occurring as a consequence of systemic complications (e.g. stroke, intracerebral hemorrhage, critical illness polyneuropathy, headache, encephalitis, cognitive impairment), COVID-19 related or otherwise, are well-documented [11,12]. However, disorders of movement in COVID-19 patients have received little attention. Commonly reported abnormal movements include ataxia, myoclonus, and tremor [13-17]. Abnormal movements such as these are often observed in neurodegenerative processes such as alzheimer's disease, frontotemporal dementia, or corticobasal degeneration. Unlike the aforementioned, a pathological basis for abnormal movements remains to be found in COVID-19 patients. While hypoxia and/or metabolic disturbances are commonplace in COVID-19 patients and could explain many acute neurological manifestations (e.g. post-anoxic myoclonus or "lance adams syndrome), these transient changes are unlikely to explain persistent or late-onset abnormal movements. The discovery of anti-neuronal antibodies to components of the basal ganglia, a region of the brain integral in control of voluntary movement, suggest that alternative mechanisms of injury exist [18]. One study even showed a bilateral decrease in presynaptic dopamine uptake on Dopamine Transporter Single Photon Emission Computed Tomography (DaT-SPECT) in a patient with new onset hypokinesia and rigidity [19]. Further, patterns of neuronal loss inconsistent with hypoxia have been observed in many areas of the brain of COVID patients [20], effectively excluding ischemia as a potential explanation. While a causal relationship remains to be established, several case reports have described the appearance of Parkinson's disease following COVID-19 infection [21-23]. Of course, this could be a simple matter of coincidence in that the onset of Parkinson's disease tends to occur within a similar age range to that of patients most adversely affected by COVID-19. It could also be that infection serves as a potentiating, rather than causal, factor in the evolution of Parkinson's disease, like what has been observed with pesticide exposure [24]. Nevertheless, these findings suggest the possibility of a causal relationship between SARS-CoV-2 infection and movement disorders.

Post-viral myoclonus is perhaps the most well-documented of known virally triggered movement disorders and was described well prior to SARS-CoV-2 [25-32]. While opsoclonus-myoclonus syndrome is common, all forms of myoclonus (i.e. focal, segmental, and generalized) have been described following viral infection. It can occur following a variety if viral infections including various arboviruses, Herpes Simplex Virus (HSV), Human Immunodeficiency Virus (HIV), Human T-Lymphotropic Virus Type 1 (HTLV-1), and measles virus. [33] published a case series of 3 patients

with myoclonus affecting the face, neck, shoulders, and upper extremities with exaggerated startle response. The acute onset of this myoclonus and its similarity to previously describe virally triggered myoclonus, as well as its presumed response to immunotherapy, led these investigators to hypothesize that a para-infectious immune-mediated mechanism could be responsible. Unfortunately, Electromyography (EMG) was not performed in any of the 3 patients and no nasopharyngeal swab was performed in 2 of 3. Further, we were unable to identify a single case report or series of COVID-19 patients where EMG was used to localize myoclonus. [34] reported a case of a 54-year-old man with continuous flexion movements of the head that began shortly following SARS-CoV-2 infection. He continued to experience unexplained jerky movements well after convalescence. Similarly, [35] reported a case of a 52-year-old patient who developed persistent generalized jerking movements and disequilibrium following infection. The report states that the patient tested positive for SARS-CoV-2 a week before onset of these symptoms. There are several other case reports describing post COVID-19 myoclonus [31-44]. While movement disorders are generally considered a rare neurological manifestation of COVID-19, their prevalence appears to be increasing. One study of 550 patients referred to a tertiary care center for movement disorders found a 60% increase in incidence of Functional Movement Disorders (FMD) during the pandemic [41].

An internal sensation of tremors or vibrations and external tremors continue to be reported by patients suffering from so-called “long-COVID." While their origin remains a mystery, proposed theories include autonomic nervous system dysfunction and peripheral nerve damage. One 50-year-old female described her experience for Becker's Hospital Review “It feels like someone put something on my bed and it's vibrating. My body is moving inside, it's jolting" Interestingly, [42] discovered an association between both self-reported COVID-19 infection and positive serology with persistent physical symptoms [43]. This has led some to suspect a functional origin of these complaints, perhaps occurring because of increased fear and anxiety related to prolonged isolation [44]. Case reports from early in the pandemic have described the onset of abnormal movements (e.g. repetitive head flexion, jerking of limbs) in patients with severe anxiety and depression determined by self-reported questionnaires [45, 46]. Of course, the possibility of coexisting functional and organic symptoms (e.g. “long-COVID" patients with a history of essential tremor prior to infection) should not be overlooked. That said, our opinion remains steadfast that functional disorders should remain diagnoses of exclusion. Whether functional or organic in origin, these sensations and abnormal movements can have significant impact on patient well-being [47]. Further investigation is paramount in effective identification and treatment of these abnormal movements.

Conclusions

Reports of movement disorders following COVID-19 infection are increasing. While the pathophysiology underlying these abnormal movements remains uncertain, the proportion of patients suffering from functional symptoms appears to be increasing.

References

1. Zhu N., et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 382.8 (2020):727-733.
2. Almqvist, J., et al. Neurological manifestations of coronavirus infections–a systematic review. *Ann clin Transl Neurol* 7.10 (2020): 2057-71
3. Arabi, Y.M, et al. Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). *Infection* 43.4 (2015): 495-501.
4. Franke, C., et al. "High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms." *Brain Behav Immun* 93 (2021): 415-419.
5. Mohkhedkar, M., et al. "Autoantigens that may explain postinfection autoimmune manifestations in patients with coronavirus disease 2019 displaying neurological conditions." *J Infect Dis* 223.3 (2021): 536-537.
6. Schiaffino, M. T., et al. "Immunoserologic detection and diagnostic relevance of cross-reactive autoantibodies in coronavirus disease 2019 patients." *J Infect Dis* 222.9 (2020): 1439-1443.
7. Neumann, B., et al. "Cerebrospinal fluid findings in COVID-19 patients with neurological symptoms." *J Neurol Sci* 418 (2020).
8. Paterson, R. W., et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain* 143.10 (2020): 3104-3120
9. Solomon I. H., et al. Neuropathological Features of Covid-19. *N Engl J Med* 383.10 (2020):989-992.
10. Post-COVID Conditions. Centers for Disease Control and Prevention.
11. Hull Hull, A., et al. "Post-acute COVID-19 functional movement disorder." *SAGE Open Med Case Rep* 9 (2021)
12. Salari, M., et al. "Movement disorders associated with COVID-19." *Parkinson's Dis 2021* (2021).
13. Salari, M., et al. "Movement disorders associated with COVID-19." *Parkinson's Dis 2021* (2021).
14. Suarez, R. P., et al. "Generalized myoclonus in COVID-19." *Neurology* 95.6 (2020): 767-772.
15. Anand, P., et al. "Myoclonus in patients with coronavirus disease 2019: a multicenter case series." *Crit Care Med* (2020).
16. Povlow, A., & Auerbach, A.J. Acute cerebellar ataxia in COVID-19 infection: a case report. *J Emerg Med* 60.1 (2021): 73-6.
17. Suarez, R. P., et al. "Generalized myoclonus in COVID-19." *Neurology* 95.6 (2020): 767-772.
18. Franke, C., et al. "High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms." *Brain Behav Immun* 93 (2021): 415-419.
19. Mendez, G. A, et al. Acute hypokinetic-rigid syndrome following SARS-CoV-2 infection. *Neurology* 95.15 (2020): 2109-18.
20. Weyhern, C. H. V., et al. "Early evidence of pronounced brain involvement in fatal COVID-19 outcomes." *The Lancet* (2020): 109.
21. Li, W.S, et al. Parkinson's disease following COVID-19: causal link or chance occurrence?. *J Transl Med* 18.1 (2020): 1-3.
22. Faber I, et al. Covid19 and Parkinsonism: A nonpostencephalitic case. *Mov Disord* (2020).
23. Mendez, G. A, et al. Acute hypokinetic-rigid syndrome following SARS-CoV-2 infection. *Neurology* 95.15 (2020): 2109-18.
24. Grossman, J. T., et al. Parkinson's disease: unanticipated sequela of an attempted suicide. *Cureus* 12.7. (2020)
25. Delucchi, V., et al. "Febrile and postinfectious myoclonus: case reports and review of the literature." *Neuropediatrics* 46.01 (2015): 026-032.
26. Blackburn, D. J., et al. "Exaggerated startle in post-infectious opsoclonus myoclonus syndrome." *Clin Neurophysiol* 129.7 (2018): 1372-1373.
27. Bhatia, K., et al. "" Isolated" postinfectious myoclonus." *J Neurol Neurosurg Psychiatry* 55.11 (1992): 1089-1091.
28. Beckham, J. D., & Kenneth L. T.. "Arbovirus infections." Continuum (Minneapolis, Minn.) 21.6 *Neuroinfectious Dis* (2015): 1599.
29. Park, J. M., et al. "Unilateral negative myoclonus caused by herpes simplex virus encephalitis." *J Mov Disord* 4.1 (2011): 49.
30. Kanjanasut, N., et al. "HIV-related opsoclonus–myoclonus–ataxia syndrome: Report on two cases." *Clin Neurol Neurosurg* 112.7 (2010): 572-574.
31. Berger, J. R., et al. "Spinal myoclonus associated with HTLV III/LAV infection." *Arch Neurol* 43.11 (1986): 1203-1204.
32. Shivji, Z. M., et al. "Subacute sclerosing panencephalitis presenting with unilateral periodic myoclonic jerks." *Can J Neurol Sci* 30.4 (2003): 384-387.
33. Suarez, R. P., et al. "Generalized myoclonus in COVID-19." *Neurology* 95.6 (2020): 767-772.
34. Garg, A., et al. "Post-acute COVID-19 functional movement disorder." *SAGE Open Med Case Rep* 9 (2021)
35. Salari, M., et al. "Movement disorders associated with COVID-19." *Parkinson's Dis 2021* (2021).

36. Smyth, D., et al. "Post-COVID-19 opsoclonus-myoclonus syndrome and encephalopathy associated with leucine-rich glioma-inactivated 1 (LGI-1) antibodies." *J Neurol Sci* (2021) 430.

37. Ishaq, H., et al. "Post-COVID opsoclonus myoclonus syndrome: a case report from Pakistan." *Front Neurol* (2021): 815.

38. Guedes, B. F., et al. "HIV-associated opsoclonus-myoclonus-ataxia syndrome: early infection, immune reconstitution syndrome or secondary to other diseases? Case report and literature review." *J NeuroVirology* 24.1 (2018): 123-127.

39. Shetty, K., et al. "Myoclonus-ataxia syndrome associated with COVID-19." *J Mov Disord* 14.2 (2021): 153.

40. Hewan, H,, et al. "Nonepileptic myoclonus in COVID-19: case report." *Neurohospitalist* 12.1 (2022): 86-89.

41. Hull, M., et al. "Increased incidence of functional (psychogenic) movement disorders in children and adults amid the COVID-19 pandemic: a cross-sectional study." *Neurol Clin Pract* 11.5 (2021): 686-690.

42. Matta, J., et al. "Association of self-reported COVID-19 infection and SARS-CoV-2 serology test results with persistent physical symptoms among French adults during the COVID-19 pandemic." *JAMA Intern Med* 182.1 (2022): 19-25.

43. Matta, J., et al. "Association of self-reported COVID-19 infection and SARS-CoV-2 serology test results with persistent physical symptoms among French adults during the COVID-19 pandemic." *JAMA Intern Med* 182.1 (2022): 19-25.

44. Schneider, S. A., et al. "Relationship between COVID19 and movement disorders: A narrative review." *Eur J Neurol* 29.4 (2022): 1243-1253.

45. Garg, A., et al. "Post-acute COVID-19 functional movement disorder." *SAGE Open Med Case Rep* 9 (2021)

46. Gilio, L., et al. "Case report: overlap between long covid and functional neurological disorders." *Front Neurol* 12 (2021).

47. Massey, D., et al. "Internal Tremors and Vibration Symptoms Among People with Post-Acute Sequelae of SARS-CoV-2: A narrative review of patient reports." *medRxiv* (2021).

Cite this article: Grossman JT. Post-acute COVID-19 Movement Disorders: Organic or Functional?. Neurol Neurorehabilit. 2022, 4(3), 25-27.