

Outpatient neurological long-COVID treatment

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Barron D. Outpatient neurological long-COVID treatment. *J Neuropathol.* 2022; 2(4):38-9.

In this study, we looked at a group of patients who had previously been infected with COVID-19 and showed signs and symptoms of neurological long-COVID.

Key Words: *Neurological involvement*

ABSTRACT

Symptoms of central and peripheral nervous system involvement are common during both the acute and long-term phases of COVID-19 infection.

INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was isolated in December 2019 in Wuhan (China) and has since caused a significant global medical issue, with an increasing number of cumulative confirmed cases. SARS-CoV-2 infection can cause mild respiratory symptoms to severe multi organ disease. In this scenario, neurological involvement has been reported in observational studies since the first cases; specifically, a study of more than 200 patients hospitalized in three COVID-19-focused hospitals in Wuhan found that more than one-third of patients had a variety of neurologic manifestations, including altered mental status and acute cerebrovascular diseases, most commonly in those with severe respiratory illness.

Reports have also linked isolated, sudden onset anosmia and ageusia to SARS-CoV-2 infection, implying that early neurological involvement may be important. SARS-CoV-2-related neurological disorders, which can affect both the Central Nervous System (CNS) and the Peripheral Nervous System (PNS), can manifest as neurological sequelae (post-infectious complications) as well as symptoms during infection (para-infectious complications). According to recent research, more than one-third of patients experience neurological symptoms while battling an infection. With the progression of the pandemic, there is evidence to suggest the emergence of an associated secondary syndrome, dubbed either post-COVID or long-COVID syndrome, in which recovering SARS-CoV-2 patients experience persistent and, in many cases, debilitating symptoms that last several months after their initial diagnosis. According to recent data, up to 20% of SARS-CoV-2 positive individuals develop long-COVID syndrome. Long-COVID is defined as "signs and symptoms developed during or following a disease consistent with COVID-19 and which continue for more than

four weeks but are not explained by alternative diagnoses" in a guideline published by the National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network, and the Royal College of General Practitioners. The NICE guidelines on long-COVID-19 include the following definitions of post-acute COVID-19: i) acute COVID (symptoms lasting up to 4 weeks); ii) ongoing symptomatic COVID (symptoms lasting 4 to 12 weeks after the start of acute symptoms); and iii) post-COVID syndrome (symptoms developed during or after an infection and continuing for more than 12 weeks). Subsequent evidence has shown that neurological involvement in long-COVID is well established. COVID-19-related neurological disorders are classified into five types: encephalopathies, inflammatory syndromes, stroke, peripheral neuropathies, and other CNS disorders. We collected demographic and acute phase course data prospectively from patients with prior COVID-19 infection who had symptoms of neurological involvement in the long-COVID phase. First, we used a multivariate logistic linear regression analysis to look at the effect of demographic and clinical data, the severity of the acute COVID-19 infection, and the hospitalization course on post-COVID neurological symptoms at three months. Second, we used unsupervised clustering to see if there was any evidence of different subtypes of neurological long COVID-19. A total of 189 patients were referred to the neurological post-COVID outpatient clinic. Clustering analysis on the most common neurological symptoms yielded two well-separated and well-balanced clusters: long-COVID type 1 includes subjects with memory disturbances, psychological impairment, headache, anosmia, and ageusia, while long-COVID type 2 includes all subjects with reported PNS involvement symptoms. The analysis of potential risk factors among demographic, clinical presentation, COVID 19 severity, and hospitalization course variables revealed that the number of comorbidities at onset, BMI, number of COVID-19 symptoms, number of non-neurological complications, and a more severe course

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Received: 3 July 2022, Manuscript No. PULNP-22-5189; Editor assigned: 5 July 2022, PreQC No. PULNP-22-5189 (PQ); Reviewed: 17 July 2022, QC No. PULNP-22-5189 (Q); Revised: 18 July 2022, Manuscript No. PULNP-22-5189 (R); Published: 27 July 2022, DOI: [10.37532/pulnp.2022.2\(4\).38-9](https://doi.org/10.37532/pulnp.2022.2(4).38-9)



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course of the acute infection were all higher for the cluster of subjects with reported symptoms related to PNS involvement. In this study, we looked at a group of patients who had previously been infected with COVID-19 and had neurological symptoms and were referred to our neurological outpatient clinic. These patients displayed symptoms suggestive of either CNS or PNS involvement. In general, we found an average age of onset of symptoms of around 57 years, as previously reported in the literature, and an equal distribution of neurological disorders in the two sexes; however, some works report a greater, albeit slight, predominance of the female sex. Our case series covers a wide range of neurological symptoms reported by patients, including anosmia and ageusia, headache, vertigo, memory disturbances, psychological symptoms, sleep disorders, and symptoms related to peripheral nervous system involvement. It is worth noting that our case series has a lower representation of patients complaining of fatigue, a disorder that has been reported in a high percentage of cases in the literature. Furthermore, fatigue and sleep disturbance were always reported as a secondary symptom by our patients and were never seen as the primary reason for visiting our outpatient clinic.

Several studies have evaluated the presence of neurological symptoms that began during the acute phase or long-COVID, but this is the first study to our knowledge that has investigated the presence of neurological long-COVID subtypes and analyzed their potential risk factors. SARS-CoV-2 can affect the nervous system in three ways: I as a direct effect of virus entry into the CNS; (ii) as a para-infectious or post-infectious immune-mediated disease; and (iii) as a secondary involvement of the CNS following the systemic effects of COVID-19. Headache is one of the first symptoms of COVID-19 infection, and it can last for months after the acute phase of the infection is over. Possible pathophysiological mechanisms of headache include SARS-CoV-2 activation of peripheral trigeminal nerve endings directly or via vasculopathy, as well as increased circulating pro-inflammatory cytokines and hypoxia. To summarize, we examined the characteristics of neurological long-COVID and presented a method for identifying well-defined patient groups with distinct symptoms and risk factors in this study. The proposed method has the potential to enable treatment deployment by identifying the best interventions and services for well-defined patient groups, thereby alleviating long-term COVID and easing recovery.