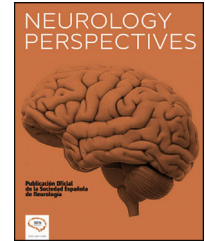




NEUROLOGY PERSPECTIVES

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EDITORIAL



Post–COVID-19 neurological symptoms

Síntomas neurológicos post-COVID-19

It was somewhat to be expected that COVID-19 would lead to several neurological manifestations during the primary infection, as well as subsequent persistent symptoms. The *Manual COVID-19 para el neurólogo general* (COVID-19 handbook for general neurologists), published by the Spanish Society of Neurology on 20 April 2020,¹ included a chapter analysing the neurological manifestations reported during the Middle East respiratory syndrome (MERS) outbreak of 2012 and the severe acute respiratory syndrome (SARS) outbreak of 2002, also caused by coronaviruses.² It was unsurprising that patients with COVID-19 may present such neurological symptoms and syndromes as headache, myalgia, confusion, and various types of neuropathies at onset or during the acute phase. However, the high frequency and specificity of anosmia as an early symptom and the association with thrombotic events and severe encephalopathies in more torpid forms of the disease was unexpected. The main evidence presaging the persistent symptoms of COVID-19 was a 2011 publication describing a series of 22 patients from Toronto, 21 of whom were healthcare workers, who developed chronic and disabling symptoms of generalised musculoskeletal pain, fatigue, depression, and sleep disorder after SARS.^{2,3} This suspicion was confirmed by clinical experience in those tragic weeks of the first wave of the COVID-19 pandemic, and especially in the time that has since passed.

Early publications and attempts at classification were very praiseworthy, but probably insufficiently reflexive. The first definitions of the condition were something of a catch-all: from severe neurological sequelae due to prolonged ICU stays to syndromes resembling fibromyalgia that emerge following an asymptomatic period after the infection, including the subjective sensation of dyspnoea, dizziness, inattention, or anosmia after mild COVID-19. This broad, nonspecific umbrella term even came to include at times such entities as persistently positive PCR results after the primary infection, reinfection with a new or the same

variant, infection or reinfection after vaccination, and the potential neurological complications.

Many scientific papers, most published open-access both for physicians and for patients, were immediately echoed in the press and social media, which have been the main sources of information, disinformation, and consolation since March 2020. One issue considered by many to be a glaring mistake, and which still creates uncertainty and damages health, is the definition of these post–COVID-19 conditions. We needed a name or a label to refer to an entity that was as yet undefined and of unknown cause. In this case, the “art of naming things,” so frequently used in medicine, was conspicuous by its absence. It was no sooner said than done: the terms chronic COVID syndrome, persistent COVID-19, or long COVID saw immediate, global success, but such designations represented a series of semantic catastrophes of inestimable iatrogenic import, as they suggest that COVID-19, or worse, SARS-CoV-2, may remain in the body for weeks or months, which is not true. The more canonical and recent designation “post-acute COVID-19 syndrome” (PACS) is more appropriate and has less negative connotations,^{4,5} though it is still not perfect. For these reasons, in this special issue of *Neurology Perspectives*, we have preferentially used the term “post–COVID-19 symptoms,” as the heterogeneity of the neurological symptoms described and the potential mechanisms of the disease, which are largely unknown, make their classification as a syndrome seem somewhat forced. We believe that this classification is more realistic and sincere, and leaves almost no connotations open to interpretation.

This clinical heterogeneity of post–COVID-19 neurological symptoms becomes apparent when we observe the spectrum of possible scenarios, which are not mutually exclusive: sequelae of prolonged hospitalisation or ICU stays, such as critical illness neuromyopathy; sequelae of neurological complications in the acute phase of the disease, ranging from long-term anosmia to the sequelae of large-vessel stroke; immune-mediated neurological conditions, such as

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Guillain-Barré syndrome; and finally, post-COVID-19 symptoms of unknown aetiology and variable clinical expression, such as dysautonomia, phenotypes resembling fibromyalgia, persistent headache, and potentially incapacitating cognitive complaints. Although these scenarios constitute well-defined categories, they may be shared by many patients, especially those with less clinically severe neurological symptoms during the acute phase, such as anosmia, headache, or myalgia. These manifestations may persist over time or even emerge after resolution of the infection, creating the mysterious constellation of symptoms unfortunately classified as chronic COVID syndrome or persistent COVID-19, which are more frequent in younger patients with milder COVID-19.

This variety of manifestations constituted a challenge when defining the focus of this special issue, as several different approaches could have been taken. Therefore, after an introduction addressing the epidemiology, pathophysiology, and classification of the condition, we opted to present it according to the main neurological symptom groups by intensity, disability, or frequency: cognitive symptoms, symptoms of possible peripheral nervous and neuromuscular origin, and persistent headache after COVID-19. We do not address sleep disorders or psychopathological and psychiatric symptoms, among others, which are frequently associated with the above-mentioned signs.

Neither do we address in detail the functional character of some of these symptoms, for which a growing body of literature is available. In this sense, some authors have suggested that less specific post-COVID-19 symptoms, classified as chronic COVID syndrome, persistent COVID-19, or long COVID, may represent the first condition defined by patients, who, unable to be attended by physicians who were unfamiliar with or dismissed the symptoms, saw their experiences reflected in social media posts by other people,^{6,7}; this is an illness collectively shaped and named by patients, distorting the way in which the natural history of a new disease is mapped out by conventional scientific methods.⁸ This possibility, far from justifying the symptoms, involves interspersed truths: many physicians have also been patients, and the information overload that we have had to deal with since the beginning of the pandemic has added a highly significant and unprecedented psychosocial component that has catalysed or perpetuated symptoms. Regarding the latter point, a key study including 26 823 patients from a French population-based cohort has been recently published (8 November 2021). Self-reported infection was associated with persistent physical symptoms, with odds ratios (OR) ranging from 1.39 (95% CI, 1.03-1.86) to 16.37 (95% CI, 10.21-26.24), with the exception of auditory symptoms and sleep disorders, whereas positive serology test results for SARS-CoV-2 were associated with persistent anosmia (OR: 2.72; 95% CI, 1.66-4.46), even when the analysis was restricted to patients who attributed their symptoms to SARS-CoV-2 infection. In conclusion, these data suggest that “persistent post-COVID-19 symptoms” seem to be more strongly associated with belief in having been infected with SARS-CoV-2 than with serological confirmation.⁹ This information may change the rules in future.

Despite the figures frequently and arbitrarily echoed by the number-crunchers, the opinion-makers, and the harbingers of tragedy (with such statements as “10% of patients,”

“approximately 500 000 people in Spain,” etc), we do not believe that post-COVID-19 symptoms will lead to a devastating new pandemic, unendurable for the Spanish National Healthcare System. Storms always pass, and biological systems tend towards self-regulation and order. The majority of patients, even those who are more exposed and more vulnerable to the above-mentioned psychosocial pressure, will improve sooner or later, whether in the hands of experts or without assistance. Life goes on, and pandemics end.

The articles in this issue were drafted between July and October 2021. Being aware that these symptoms are still in process of being defined, “symptoms in the mist” if we may permit ourselves the expression, we deemed it appropriate, and above all necessary, to publish this special issue on the main post-COVID-19 neurological symptoms. Considering the limited references in the literature, and aware that we will soon have answers from relevant studies that have already been published^{10,11,12} or are underway, we asked all the authors to make an effort to review, organise, clarify, and even forecast groups of symptoms. All of those involved, both authors and editors, are aware of the ephemeral value of this collective task, but establishing some degree of order amongst this chaos is well worth the time and dedication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neurop.2021.11.001>.

References

1. Manual COVID-19 para el neurólogo general. In: Ezpeleta D, García Azorín D, editors. DL: M-11429-2020. Ediciones SEN; 2020. editores. ISBN: 978-84-946708-3-1.
2. García-Moncó JC. Cuadros clínicos neurológicos asociados a la infección por otros coronavirus. In: Ezpeleta D, García Azorín D, editors. Manual COVID-19 para el neurólogo general. Ediciones SEN; 2020. editores. ISBN: 978-84-946708-3-1. DL: M-11429-2020.
3. Moldofsky H, Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. *BMC Neurol*. 2011 Mar 24;11:37. <https://doi.org/10.1186/1471-2377-11-37>.
4. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021 Apr;27(4):601–15. <https://doi.org/10.1038/s41591-021-01283-z>.
5. Moghimi N, Di Napoli M, Biller J, Siegler JE, Shekhar R, McCullough LD, et al. The neurological manifestations of post-acute sequelae of SARS-CoV-2 infection. *Curr Neurol Neurosci Rep*. 2021 Jun 28;21(9):44. <https://doi.org/10.1007/s11910-021-01130-1>.
6. Callard F, Perego E. How and why patients made Long Covid. *Soc Sci Med*. 2021 Jan;268:113426. <https://doi.org/10.1016/j.socscimed.2020.113426>.
7. Rushforth A, Ladds E, Wieringa S, Taylor S, Husain L, Greenhalgh T. Long Covid - The illness narratives. *Soc Sci Med*. 2021 Oct;286:114326. <https://doi.org/10.1016/j.socscimed.2021.114326>.
8. Callard F. Epidemic Time: Thinking from the Sickbed. *Bull Hist Med*. 2020;94(4):727–43. <https://doi.org/10.1353/bhm.2020.0093>.

9. Matta J, Wiernik E, Robineau O, Carrat F, Touvier M, Severi G, et al. Pratiques, Relations et Inégalités Sociales en Population Générale Pendant la Crise COVID-19-Sérologie (SAPRIS-SERO) Study Group. 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.* 2021 Nov 8 <https://doi.org/10.1001/jamainternmed.2021.6454>.
10. Augustin M, Schommers P, Stecher M, Dewald F, Gieselmann L, Gruell H, et al. Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. *Lancet Reg Health Eur.* 2021 Jul;6:100122. <https://doi.org/10.1016/j.lanepe.2021.100122>.
11. Beghi E, Giussani G, Westenberg E, Allegri R, Garcia-Azorin D, Guekht A, Frontera J, Kivipelto M, Mangialasche F, Mukaetova-Ladinska EB, Prasad K, Chowdhary N, Winkler AS. Acute and post-acute neurological manifestations of COVID-19: present findings, critical appraisal, and future directions. *J Neurol.* 2021 Oct;21:1–10. <https://doi.org/10.1007/s00415-021-10848-4>.
12. Camargo-Martínez W, Lozada-Martínez I, Escobar-Collazos A, Navarro-Coronado A, Moscote-Salazar L, Pacheco-Hernández A, et al. Post-COVID 19 neurological syndrome: implications for sequelae's treatment. *J Clin Neurosci.* 2021 Jun;88:219–25. <https://doi.org/10.1016/j.jocn.2021.04.001>.

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