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Editorial article

Post-COVID syndrome. The never ending challenge[☆]

Síndrome post-COVID. El desafío continúa

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Shortly after the first wave of the COVID-19 pandemic, we began to observe that some patients had persistent symptoms after recovery from the acute infection. These clinical manifestations could constitute a new post-infectious syndrome, similar to what occurs in other infections such as those caused by Epstein-Bar, *Coxiella burnetii* or Lyme disease.¹ At present it is difficult to distinguish whether these symptoms are related to the virus itself, to indirect effects of the disease or to the impact of the pandemic situation. The term #LongCOVID was proposed as a Twitter hashtag in May 2020 by affected patient groups to define this condition.

Regardless of their relationship to SARS-CoV-2, direct or otherwise, these disorders have a medium- and long-term health impact. Reports in our country show that only 40% of patients have returned to work 2–3 months after infection.² Population-based studies in the United States comparing cohorts of patients hospitalized for COVID-19 with patients hospitalized for other causes (including cohorts with viral infections), demonstrate a greater need for subsequent medical care,³ and even an increase in the frequency of hospital readmission and mortality.⁴

With more than 177 million people infected by SARS-CoV-2 worldwide⁵ –some 4.5 million in Spain–, even with conservative incidences of these clinical disorders of 10–20%, we estimate that it could affect some 450,000–900,000 people in our country, a relevant health problem that requires a response both in scientific and healthcare terms.

In our opinion, the available evidence is so heterogeneous that its interpretation is very difficult. With more than 18,000 publications and 22 meta-analyses,⁶ different terms are exchanged in the literature, such as *long-COVID*, *post-acute COVID-19 syndrome* or *post-COVID conditions*, with the absence of a standardized definition, which implies the inclusion of different clinical features.

In an attempt to standardize terms, CDC and WHO propose the generic use of “*post-COVID conditions*” as a broad umbrella for the health consequences that persist 4 weeks after the acute infection.^{5,7} In contrast, the UK *National Institute for Health and*

*Care Excellence (NICE)*⁸ proposes the term “*long-COVID*” as an operational definition, which encompasses persistent symptoms 4 weeks after acute infection in the absence of an alternative aetiological diagnosis. This term would include the “*ongoing symptomatic COVID-19*” for signs and symptoms between 4 and 12 weeks after the acute infection and “*post-COVID syndrome*” for persistence of more than 12 weeks.

This definition contributes two relevant points. First of all, the duration of symptoms of 12 weeks after infection to establish the diagnosis of post-COVID syndrome. In our experience and in line with the literature, the persistence of symptoms in the first 4–8 weeks after infection is common and multifactorial, with a tendency to progressive resolution, so that, although arbitrarily established, the time frame of 12 weeks allows to outline a more differentiated and COVID-19-related clinical picture. The second point of interest in this definition is the inclusion of “no alternative diagnosis”. After COVID-19, the signs and symptoms that these patients manifest, even if they are new-onset, may be related to other processes, either independent or triggered by the infection. Identifying these “alternative diagnoses” is essential for the characterisation of the post-COVID syndrome symptomatology and for the development of the care and treatment approach.

From a practical point of view, these post-COVID clinical manifestations could be grouped into the following categories:

- 1 Sequelae: consequence of established organ damage following acute disease. Thrombotic, psychiatric, neurological, pulmonary, cardiac, renal and reproductive events are the most common.^{9,10} These manifestations would probably not belong to a post-infectious syndrome as such, since they reflect an established organ damage related to the pathophysiology of the acute infection.
- 2 Derived from the hospitalisation itself, and which would be common with other diseases, such as post-ICU syndrome, or secondary to prolonged hospitalisation, among which neuromuscular involvement, fatigue, cognitive or psychiatric disorders stand out. It is important to point out that isolation measures and the restriction of visits in this disease can have a greater impact than conventional hospitalization.
- 3 Decompensation of previous chronic diseases.

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- 4 Onset of a new disease, COVID-19 infection could act as a trigger for other diseases, whether autoimmune, metabolic or psychiatric.
- 5 Pharmacological toxicity: although little reported in the literature, it is important to consider the effects of treatments administered during hospitalisation.

Clinical manifestations that cannot be grouped into these categories and that persist over time would constitute the “*post-COVID syndrome*” as a post-infectious syndrome per se. Defining this symptomatology with the data from the published series is complex, given that only one third of them include a face-to-face clinical interview, and the type of assessment performed on patients is very different.

The most common symptomatology, reported by WHO and CDC,^{5,7} includes fatigue as the most characteristic symptom (present in 60–70%), defined as intense tiredness that interferes with activities of daily living. Of unknown pathophysiology, it has been compared with myalgic encephalomyelitis or chronic fatigue syndrome. Dyspnoea, with oximetry, radiological examination and normal respiratory function, frequently associated with cough and nonspecific chest pain, is characteristic and prolonged over time. Regarding the neurocognitive area, there is a decrease in the ability to concentrate (*brain fog*), memory alterations, headache and persistence of ageusia and anosmia. Anxiety and depressive symptoms, as well as sleep disturbances, are very common. Other manifestations are hair loss, arthralgia, myalgia, tachycardia, or gastrointestinal rhythm disturbances, although more than 50 different symptoms have been described.^{10–13}

Any patient can develop long COVID, regardless of the severity of the initial infection, even asymptomatic patients. Although the series are contradictory,¹⁴ it appears that the severity of acute infection may increase the risk. The overlap of symptoms and the definitions used may explain these discrepancies. Age does not seem to be a risk factor, but gender does, with a prevalence of women. The association with co-morbidity, which may act as a confounding factor in the interpretation of symptoms, is unclear.¹⁵ The influence of new viral variants or vaccination on the incidence, characteristics or duration of post-COVID syndrome is not determined.

In terms of incidence, our experience shows that approximately half of the nearly 300 patients hospitalised for COVID-19 and systematically evaluated (with clinical, laboratory, radiological and respiratory function tests), 12–14 weeks after infection had some of these symptoms, generally mild, but interfering with quality of life.¹⁰ The incidence published in the literature is highly variable and influenced by the great heterogeneity of the series, making the value of published meta-analyses questionable⁶: from 60 to 80% have been described at 8 weeks after infection^{16,17} and from 40 to 50% at 10–14 weeks.^{18,19} Recently, a large prospective cohort of more than 1200 patients described the presence of some symptoms in more than 68% and 49% of patients at 6 and 12 months, respectively.²⁰

At present there is no clear-cut idea of the prognosis. Some studies report progressive symptom improvement at follow-ups extended to one year, although with some fluctuating symptoms.²⁰

Optimal and systematic management of patients at this time is unclear. Clinical trials examining medium and long-term results are advisable. Trivialisation by professionals (*medical gaslighting*) of these “medically unexplained symptoms” should be avoided, as it can lead to frustration and loss of trust in the health system by patients. A comprehensive clinical evaluation, avoiding unnecessary ancillary examinations, and realistic information to patients can help to minimize this problem. The creation of support groups and social connection can be useful for the care of these patients.

In the light of the available evidence, and pending the results of future systematised studies, a reasonable and efficient approach to the challenge that these post-COVID disorders pose to our national health system should be based on:

- 1 Establish coordinated clinical pathways in the health system, with integration of primary care and specialised hospital care resources and the creation of a hospital-based monographic COVID clinic. Patients with prolonged hospital admission or with suspected sequelae at discharge would be systematically evaluated in the COVID clinic, with a follow-up adapted to the needs of each case. Hospitalised patients with no suspected sequelae but with moderate to severe involvement would be assessed by telephone using a structured questionnaire 12 weeks after infection; in case of persistent symptoms, a protocol-based assessment in primary care would be indicated. Based on this assessment, the patterns for referral to the COVID clinic (either in person or online) or follow-up in primary care can be agreed upon. Finally, for patients without initial hospital admission, an evaluation would be carried out in primary care at the request of the patient.

Coordination between primary care and specialised hospital care, as well as the incorporation of telemedicine, would allow for efficient care with optimisation of resources.

- 2 Training of professionals that allows updating the knowledge generated, agreeing on common clinical protocols and coordinating the different levels of care.
- 3 Information to patients about post-COVID scenarios. It should include both the description of the most common symptoms, the warning symptoms or medical consultation, general measures for symptom control, realistic goals in relation to the prognosis and the gradual return to an active employment situation.

In terms of prevention, vaccination promotion campaigns could include messages indicating that preventing COVID-19 also prevents subsequent persistent symptoms with potential long-term health effects.²¹

In conclusion, post-COVID syndrome is a relevant health problem that requires a global response from society in terms of research, health management and information.

Investment in research, both basic and clinical, with the creation of large inter-hospital cohorts, as has been done with HIV infection, is a cornerstone. The PHOSP-COVID cohort²² has been established in the UK and is currently monitoring more than 10,000 patients after COVID infection. In this sense, the generous involvement of scientific societies is very important. Simultaneously, an increase in health resources is needed, with adequate management of these in order to optimise them, guaranteeing the appropriate care for the population. Dissemination of reliable information to patients and the population at large that combats the negative effects of misinformation should be encouraged.

Let us ensure that the aftermath of COVID-19 does not become the “*brain fog*” of our national health system in the next decade.

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Conflict of interests

The authors declare no conflicts of interest.

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References

- Hickie I, Davenport T, Wakefield D, Vollmer-Conna U, Cameron B, Vernon SD, et al. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *BMJ*. 2006;333:575–8.
- Bouza E, Moreno Cantón, De Lucas Ramos P, García-Botella A, García-Lledó A, Gómez-Pavón J, et al. [Post-COVID syndrome: a reflection and opinion paper]. *Rev Esp Quimioter*. 2021;34:269–79.
- Daugherty SE, Guo Y, Heath K, Dasmariñas MC, Jubilo KG, Samranvedhya J, et al. Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ*. 2021;373:1–12.
- Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. *BMJ*. 2021:693–6.
- CDC [Accessed 3 September 2021]. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects.html>, 2020.
- Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cua-pio A. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep*. 2021;11:16144–6.
- Post COVID-19 condition: WHO supports standardization of clinical data collection and reporting (n.d.) [Accessed 3 September 2021]. Available from: <https://www.who.int/news/item/12-08-2021-post-covid-19-condition-who-supports-standardization-of-clinical-data-collection-and-reporting>.
- Overview | COVID-19 rapid guideline: managing the long-term effects of COVID-19 | Guidance | NICE (n.d.) [Accessed 3 September 2021]. Available from: <https://www.nice.org.uk/guidance/ng188>.
- Moreno-Perez O, Merino E, Alfayate R, Torregrosa ME, Andres M, Leon-Ramirez JM, et al. Male pituitary-gonadal axis dysfunction in post-acute COVID-19 syndrome-Prevalence and associated factors: a Mediterranean case series. *Clin Endocrinol (Oxf)*. 2021:14537–9.
- Moreno-Pérez O, Merino E, Leon-Ramirez JM, Andres A, Ramos JM, Arenas-Jiménez J. Post-acute COVID-19 syndrome. Incidence and risk factors: a Mediterranean cohort study. *J Infect*. 2021;82:372–8.
- Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27:601–15.
- Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. *BMJ*. 2021;374:1648–51.
- Romero-Duarte A, Rivera-Izquierdo M, Guerrero-Fernández de Alba I, Pérez-Contreras M, Fernández-Martínez NF, Ruiz-Montero R, et al. Sequelae, persistent symptomatology and outcomes after COVID-19 hospitalization: the ANCOHVID multicentre 6-month follow-up study. *BMC Med*. 2021;19:12916–9.
- Al-Aly A, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*. 2021;594:259–64.
- Ghosn J, Piroth L, Epaulard O, Le Turnier P, Mentré F, Bachelet D, et al. Persistent COVID-19 symptoms are highly prevalent 6 months after hospitalization: results from a large prospective cohort. *Clin Microbiol Infect*. 2021;27:1041–4.
- Carfi A, Bernabei R, Landi F, Gemelli M. Persistent symptoms in patients after acute COVID-19. *JAMA*. 2020;324:603–5.
- Carvalho-Schneider C, Laurent E, Lemaignan A, Beaufile E, Bourbao-Tournois C, Laribi S, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect*. 2021;27:258–63.
- Arnold DT, Hamilton FW, Milne A, Morley AJ, Viner J, Attwood M, et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. *Thorax*. 2021;76:399–401.
- Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect*. 2020;81:e4–90.
- Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet*. 2021;398:747–58.
- Antonelli M, Penfold RS, Merino J, Sudre CH, Molteni E, Berry S, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. *Lancet Infect Dis*. 2021. [http://dx.doi.org/10.1016/S1473-3099\(21\)00460-6](http://dx.doi.org/10.1016/S1473-3099(21)00460-6).
- PHOSP (n.d.) [Accessed 3 September 2021]. Available from: <https://www.phosp.org/>.