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The effect of age on cognitive impairment associated with post COVID-19 syndrome

To the editor

Approximately 15% of patients infected with SARS-CoV-2 suffer from a disorder called “post COVID-19 syndrome”, recently defined by the World Health Organization as a condition that “occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last over 2 months and cannot be explained by an alternative diagnosis.” Among the most common symptoms of post COVID-19 syndrome are fatigue, headache, respiratory difficulties, and cognitive dysfunction, although more than 200 symptoms have been described, mainly in female patients, aged around 40-50 years and who have had mostly mild or asymptomatic COVID-19 (Davis et al., 2021). Of all, cognitive symptoms are the ones that most often concern patients, as they frequently interfere with their work and social activities.

Several studies have been carried out to try to clarify the cognitive profile of patients with post COVID-19 syndrome, and several of them have found impairment in attention, processing speed, executive functions, visuospatial skills, and verbal and working memory (for a revision, see Bertuccelli et al., 2022). However, the results are inconsistent, since other studies, such as that of Dressing et al. (2022), failed to find impairments despite the breadth of the neuropsychological battery applied to the patients. Furthermore, many of these studies do not differentiate between patients with post COVID-19 syndrome (without structural brain damage) and those with sequelae of COVID-19 (with structural brain damage often due to the presence of hypoxia and with a different patient profile, being mostly elderly males) (Premraj et al., 2022) and samples tend to be small, which prevents comparisons between patients themselves.

The purpose of our study was, therefore, to identify the cognitive features of a large sample of patients with a diagnosis of post COVID-19 syndrome through a comprehensive neuropsychological evaluation that assessed the superior cognitive functions with the following tasks: attention (BTA), processing speed (Stroop words and colors, digit span forward), verbal (TAVEC), visual (ROCF recall), prospective (test ad hoc) and working (digit span backward) memory, visuospatial skills (ROCF copy) executive functions (Hanoi Tower, Stroop W-C, WAIS-IV Matrix reasoning, phonological, actions and excluded verbal fluency), and language (semantic verbal fluency, BETA object and actions naming tasks).

Two hundred and fourteen patients (male/ female = 32/182; mean age ± standard deviation = 47.48 ± 7.35, ranged 26-64 years) took part in this research. All of them had a confirmed diagnosis of COVID-19 of at least four months prior to participation in the study, presented neurological complaints that appeared during or after SARS-CoV-2 infection and had a confirmed diagnosis of post COVID-19 syndrome or were in the process of diagnostic confirmation. None of them had other disease that could lead to cognitive problems, nor history of alcohol or drug abuse. The evaluations were conducted online to comply with sanitary recommendations.

The raw scores were converted into standardized or scalar scores according to the Neuronorma project (Peña-Casanova et al., 2009). Z-Scores between -1.5 and -2.99 (corresponding to 3 to 6 scalar scores) were considered mild impaired, while Z-scores under -3 SD (corresponding to scalar scores under 3) were considered severe impaired for this purpose.

The results show alterations in at least one neuropsychological test in more than 85% of the patients, although no statistical differences were found between hospitalized and non-hospitalized patients, which rules out that these deficits are a consequence of the severity of the disease. On the contrary, the presence and severity of the cognitive impairments seem to be related to the age of the patients, although in a direction opposite to that expected, i.e., younger patients show impairment in some cognitive domain more frequently than older ones, and the severity of this impairment is greater in these younger patients. This result has been corroborated both by correlation analysis and by comparisons between groups of patients according to their age (young: N=29, ranged 26 to 39 years; middle age: N=97, ranged 40 to 49 years; senior: N=88, ranged 50 to 64 years). This outcome, a priori contrary to expectations, since younger age usually induces a better prognosis in virtually all disorders with cognitive deficits, seems to support one of the causal hypothesis of post COVID-19 syndrome, according to which many SARS-CoV-2-infected patients have antibodies specific for the ACE2 enzyme. Binding of SARS-CoV-2 to ACE2 results in cytokine storming and increased inflammation during SARS-CoV-2 infection (Arthur et al., 2021). Since aging affects the immune system by weakening it, the autoimmune response will also be weaker in seniors than in young patients.

Regarding the different cognitive functions, attention shows the greatest deficit, regardless of the age of the patients. It is followed by processing speed, verbal memory and verbal fluency, in which the effect of age is clearly observed, with a higher percentage of patients with altered scores and a higher percentage of scores corresponding to severe deficits in the young group. Scores in executive functions and visual and working memory also show this effect of age. The time of evolution of the disorder, as well as cognitive reserve, had a little impact on the cognitive performance of our patients.

In conclusion, the results presented here reveal that a high percentage of patients with post COVID-19 syndrome exhibit deficits in some cognitive ability, which corroborates their subjective complaints. In addition, the youngest patients were those who showed the most marked and heterogeneous cognitive impairment, while the oldest patients maintained their cognitive functions preserved to a greater extent with only a mild impairment in attention and speed processing. Precisely
both functions were the cognitive processes that are most deficient and homogeneously identified across the different age subgroups.

Data availability

The data that support the findings of this study are available from the corresponding author, (gonzaleznmaria@uniovi.es) upon reasonable request.

Declaration of Competing Interest

The authors report there are no competing interests to declare.

Funding

This research has not received specific support from public sector agencies, commercial sector or non-profit entities.

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