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ORIGINAL ARTICLE

Cognitive decline among individuals with history of mild symptomatic SARS-CoV-2 infection: A longitudinal prospective study nested to a population cohort

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Abstract

Background and purpose: Neurological complications of SARS-CoV-2 infection are noticed among critically ill patients soon after disease onset. Information on delayed neurological sequelae of SARS-CoV-2 infection is nil. Following a longitudinal study design, the occurrence of cognitive decline among individuals with a history of mild symptomatic SARS-CoV-2 infection was assessed.

Methods: Stroke- and seizure-free Atahualpa residents aged ≥40 years, who had pre-pandemic cognitive assessments as well as normal brain magnetic resonance imaging and electroencephalogram recordings, underwent repeated evaluations 6 months after a SARS-CoV-2 outbreak infection in Atahualpa. Patients requiring oxygen therapy, hospitalization, and those who had initial neurological manifestations were excluded. Cognitive decline was defined as a reduction in the Montreal Cognitive Assessment (MoCA) score between the post-pandemic and pre-pandemic assessments that was ≥4 points greater than the reduction observed between two pre-pandemic MoCAs. The relationship between SARS-CoV-2 infection and cognitive decline was assessed by fitting logistic mixed models for longitudinal data as well as exposure-effect models.

Results: Of 93 included individuals (mean age 62.6 ± 11 years), 52 (56%) had a history of mild symptomatic SARS-CoV-2 infection. Post-pandemic MoCA decay was worse in seropositive individuals. Cognitive decline was recognized in 11/52 (21%) seropositive and 1/41 (2%) seronegative individuals. In multivariate analyses, the odds for developing cognitive decline were 18.1 times higher among SARS-CoV-2 seropositive individuals (95% confidence interval 1.75–188; p = 0.015). Exposure-effect models confirmed this association (β = 0.24; 95% confidence interval 0.07–0.41; p = 0.006).

Conclusions: This study provides evidence of cognitive decline among individuals with mild symptomatic SARS-CoV-2 infection. The pathogenesis of this complication remains unknown.

KEYWORDS
cognitive decline, coronavirus-19, COVID-19, Montreal Cognitive Assessment, SARS-CoV-2

INTRODUCTION

With more than 100 million people infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) worldwide, descriptions of neurological manifestations during the acute phase of coronavirus disease 2019 (COVID-19) are on the rise [1–3]. In general, these have been classified into three groups: stroke, acute encephalitis (or diffuse encephalopathy) and peripheral/cranial neuropathies [4]. In addition, many patients develop anosmia–ageusia or non-specific headaches [5]. The pathogenetic mechanisms involved in the development of neurological complications of COVID-19 are complex and not fully understood thus far [6,7].

Strokes—ischaemic or haemorrhagic—have been mostly associated with cardiogenic brain embolism, large artery disease and vasculitis [8]. Acute encephalitis and encephalopathy may occur as a result of the cytokine release syndrome [9] or due to direct invasion of the central nervous system by SARS-CoV-2 since the receptor used by the virus for cell entry—angiotensin-converting enzyme 2—is expressed in neurons and glial cells [10]. Neuropathies often occur due to peripheral/cranial nerve damage secondary to a post-infectious inflammatory response observed soon after the acute phase of the disease [11].

Neurological manifestations associated with SARS-CoV-2 infection often occur during the second week of disease onset and are more commonly observed among critically ill patients [1–5]. While some reports have described delayed psychiatric sequelae after COVID-19 [12,13] and others have hypothesized the potential occurrence of delayed neurological manifestations [14–16], no study has systematically assessed the occurrence of cognitive decline among COVID-19 survivors.

The Atahualpa Project, a population-based prospective cohort study designed to investigate factors influencing the burden of neurological diseases among community dwellers living in rural Ecuador, was started in 2012 [17]. Since its inception the adult population of Atahualpa has undergone tests for assessing cognitive performance, cerebrovascular diseases, epilepsy, sleep disorders and other conditions of interest [18–21]. Atahualpa was severely struck by the SARS-CoV-2 pandemic, as evidenced by a mortality rate of 21.6 per 1000 population during March–April 2020 [22], a seroprevalence of 45% among survivors [23] and an incidence rate ratio of 7.4 per 100 person-months of potential virus exposure [24]. Taking the unique opportunity of the well-established Atahualpa Project cohort, the present longitudinal prospective study aimed to assess the occurrence of cognitive decline 6 months after an episode of mild symptomatic SARS-CoV-2 infection.

METHODS

Study population

The population of Atahualpa is homogeneous in terms of ethnicity, socioeconomic status and lifestyles [17]. Migration of villagers is minimal, providing an ideal scenario for the conduction of cohort studies [25]. Atahualpa residents aged ≥40 years were eligible for the present study if they fulfilled the following criteria: (1) were continuously enrolled in the Atahualpa Project for at least 5 years before the SARS-CoV-2 pandemic; (2) had a normal baseline magnetic resonance imaging (MRI) of the brain and a normal electroencephalogram (EEG) recording before the pandemic; (3) had two evaluations of cognitive performance by means of the Montreal Cognitive Assessment (MoCA) before the pandemic; (4) no history of seizures/epilepsy; (5) a stroke-free status; (6) investigation of SARS-CoV-2 antibodies in two rounds performed on May and June, 2020; (7) no administration of corticosteroids and no need for oxygen therapy or hospitalization among those with COVID-19-related clinical manifestations; and (8) no clinically evident neurological or psychiatric manifestations up to September 2020. In addition, all previously seronegative individuals (in May and June) underwent a repeated lateral-flow-based antibody testing (BIOHIT Health Care Ltd, Cheshire, UK) at the time of this study to assess for more recent infections (subjects with recent infections were not included).

Background data

Before the SARS-CoV-2 pandemic, all participants had undergone periodic clinical evaluations (including interviews and examinations aimed to assess the history of seizures/epilepsy and neurological deficits) as well as a brain MRI using a Philips Intera 1.5- T MR scanner (Philips Medical Systems, Eindhoven, The Netherlands) and a 1-h scalp EEG using a Nihon Kohden EEG-1200 digital machine (Nihon Kohden Corporation, Tokyo, Japan), which was performed using the international 10–20 electrode configuration with the addition of T1 and T2 electrodes [26]. MRIs had been performed during the first year after enrolment in the Atahualpa Project (2013–2018) and EEG recordings were obtained in 2016 and 2017. Cognitive performance had been evaluated twice (first round from 2013 to 2015, and second round from 2017 to 2019) by use of the Spanish version of the MoCA [19].

Study design

Following a longitudinal prospective design, this study investigated the presence of cognitive decline in community-dwelling middle-aged and older adults with and without a history of mild symptomatic SARS-CoV-2 infection fulfilling the above-mentioned inclusion criteria. To reduce misclassifications, cognitive decline was defined as a worsening in the post-pandemic MoCA score ≥4 points compared to the reduction experienced between pre-pandemic baseline and follow-up MoCA scores. This cutoff was selected to stratify individuals based on our historical experience with MoCA decay (before the pandemic) in individuals enrolled in the Atahualpa Project, which showed that the mean decrease in cognitive performance was ≤2 points in the MoCA score after almost 4 years of follow-up [19]. The study protocol

and comprehensive informed consent—signed by all participants—were approved by the institutional review board of Universidad Espíritu Santo, Ecuador (FWA 00028878).

Studies performed for the current survey

Six months after the start of the SARS-CoV-2 pandemic in Atahualpa (September 2020), individuals eligible for being included in this study underwent repeated clinical interviews, evaluation of cognitive performance and EEG recordings. All subjects with a post-pandemic cognitive decline underwent a new MRI of the brain to assess if the observed changes in MoCA scores were related to structural brain lesions.

Clinical interviews included assessment of possible new seizure episodes or any other neurological complaint between June and September 2020. Variables known to modify cognitive performance—already investigated in individuals enrolled in the Atahualpa Project cohort—were updated for the present study. These were used for adjustment in multivariate models and included demographics, cardiovascular risk factors (obesity, high blood pressure and high fasting glucose) stratified according to criteria proposed by the American Heart Association [27], sleep quality and symptoms of depression (assessed using the Pittsburgh Sleep Quality Index [28] and the depression axis of the Depression Anxiety Stress 21 scale [29], respectively). Education was not used as a covariate to avoid collinearity, since the MoCA gives one extra point to individuals with low education level.

Montreal Cognitive Assessments were taken by a trained physician (B.Y.R.) following previously described standards [19]. The test (www.mocatest.org, © Z. Nasreddine MD, version November 7, 2004) evaluates several cognitive domains, including visuospatial-executive, naming, attention and calculation, language, verbal abstraction, delayed recall and orientation. The maximum MoCA score is 30 points (an additional point is given to persons with ≤12 years of education) [30]. A cutoff score for defining cognitive impairment was not used due to the poor validity of established cutoffs in poorly educated populations [31]. All men were breathalysed before the MoCA to ensure a blood alcohol content reading of 0.0%, and those who tested positive were requested to stay sober and were invited after 72 h. Women were not breathalysed because their alcohol intake is nil [32].

Repeated EEG recordings were performed with the same equipment and protocol as used for pre-pandemic EEGs [26], with the addition of biosafety recommendations for the practice of this examination at the time of the SARS-CoV-2 pandemic [33]. One-hour scalp EEGs included eye opening, eye closure, hyperventilation, photic stimulation, wakefulness and sleep (when possible). Examinations were reviewed by epilepsy-board certified neurologists (S.W., N.P.I.) blinded to clinical data and SARS-CoV-2 serological status. The presence or absence of a posterior-dominant alpha rhythm, eye opening reactivity, background rhythm frequency and amplitude, the effect of hyperventilation and photic stimulation, focal abnormalities (focal slowing or epileptiform discharges) and generalized slowing were tabulated.

Statistical analyses

Data analyses were carried out by the study biostatistician (R.M.M.) using STATA version 16 (College Station, TX, USA). In univariate analyses, continuous variables were compared by linear models and categorical variables by χ^2 or the Fisher exact test as appropriate. Changes in the MoCA score between baseline/follow-up pre-pandemic and post-pandemic tests were assessed by means of linear mixed models for longitudinal data, adjusted for all covariates. The independent relationship between a history of mild symptomatic SARS-CoV-2 infection and changes over time in the MoCA score—as the dependent variable—was assessed by fitting multivariate generalized linear models with a logistic link. Marginal means were used to estimate the size of the difference of having lower scores in the post-pandemic MoCA in SARS-CoV-2 seropositive subjects compared with seronegative ones, after adjusting for all covariates.

A power analysis was carried out to evaluate the minimum size of the difference needed to evaluate a post-pandemic MoCA ≥4 points, and with 80% power at the 0.05 significance level and with the same distribution of seropositivity, the minimum odds ratio was found to be 7.7 with the sample size available.

The independent association between history of mild symptomatic SARS-CoV-2 infection and cognitive decline was assessed by fitting a multivariate logistic regression model, adjusted for demographics, cardiovascular risk factors, sleep quality and symptoms of depression. To get more insights into the relationship between exposure (mild symptomatic SARS-CoV-2 infection) and outcome (cognitive decline), a treatment (exposure) effects methodology was used, which computed the propensity score of MoCA decline to minimize the effect of covariates on SARS-CoV-2 serological status.

RESULTS

Ninety-six individuals actively enrolled in the Atahualpa Project as of August 2020 fulfilled the above-mentioned inclusion criteria. Of them, two women (aged 74 and 77 years) seroconverted to positive after being tested seronegative in May and June (meaning a more recent infection), and one previously seronegative woman (74 years old) declined consent. These three subjects were excluded from analyses, leaving 93 individuals evaluated with repeated MoCAs and EEG recordings. Of them, 52 (56%) had a history of mild symptomatic SARS-CoV-2 infection between March and May. The remaining 41 (44%) individuals did not have clinical manifestations and were seronegative for SARS-CoV-2. Asymptomatic seropositive and symptomatic seronegative subjects were not included in this study to reduce the risk of misclassifications.

The mean age of participants was 62.6 ± 11 years (median 64 years), 59 (63%) were women, 22 (24%) had a body mass index ≥30 kg/m^2, 30 (32%) had blood pressure levels ≥140/90 mmHg, 25 (27%) had fasting glucose ≥126 mg/dl, 32 (34%) had a poor sleep quality, and nine (10%) had symptoms of depression. Table 1 depicts characteristics of participants across categories of SARS-CoV-2 seropositivity (univariate analysis).

The mean (±SD) score in the baseline MoCA was 23 ± 4.2 and that in the follow-up MoCA was 21.6 ± 3.9 points. Both examinations were taken before the SARS-CoV-2 pandemic; the total person-years of follow-up was 303.1 (95% confidence interval [CI] 284.8–321.4 years). The decay between pre-pandemic baseline and follow-up MoCA scores was significant in univariate analysis (p = 0.020). Overall, 61 (65%) individuals had lower MoCA scores in the follow-up, 23 (25%) had the same score and the remaining nine (10%) had higher scores.

The mean (±SD) score in the MoCA performed 6 months after the start of the SARS-CoV-2 pandemic in the village was 20.2 ± 4.2 points. The total person-years of follow-up from the last pre-pandemic test was 253.4 (95% CI 242.5–264.2 years). Overall, the mean MoCA score was significantly different between the pre-pandemic follow-up and the post-pandemic tests in univariate analysis (21.6 ± 3.9 vs. 20.2 ± 4.2; p = 0.020).

Stratification of individuals according to their serological status disclosed that the mean pre-pandemic MoCA follow-up score was similar across the 52 individuals who later became seropositive (21.7 ± 4 points) and the 41 who remained seronegative (21.5 ± 5 points). However, the mean post-pandemic MoCA score was significantly lower among seropositive individuals (21.7 ± 4 vs. 19.6 ± 4.2; p = 0.010) but not in their seronegative counterparts (21.5 ± 5 vs. 21 ± 4; p = 0.618). In other words, the post-pandemic MoCA decay was mostly noticed in individuals with a history of mild symptomatic SARS-CoV-2 infection. Mixed models for longitudinal data, adjusted for all covariates, confirmed no difference in the size of the decay between baseline and follow-up pre-pandemic MoCAs among the group of individuals who later became SARS-CoV-2 positive compared to those who remained seronegative (β = −1.05; 95% CI −2.57–0.61; p = 0.174). However, this difference became significant in the post-pandemic MoCA, where individuals with a history of mild symptomatic SARS-CoV-2 infection had a marked decay in marginal MoCA scores (Figure 1).

Overall, 12 (13%) individuals had a reduction in the post-pandemic MoCA that was ≥4 points larger than the reduction that occurred between two pre-pandemic MoCA assessments. This was twice as large as the decay experienced between the pre-pandemic baseline and the follow-up MoCAs in the overall Atahualpa population. Cognitive decline was observed in 11 of 52 (21%) individuals with a history of mild symptomatic SARS-CoV-2 infection, and only in one of 41 (2%) asymptomatic seronegative individuals (p = 0.010). A multivariate logistic regression model demonstrated an independent association between a history of mild symptomatic SARS-CoV-2 infection and post-pandemic cognitive decline ≥4 points (odds ratio 18.1; 95% CI 1.75–188; p = 0.015). Symptoms of depression could not be used in this model because of collinearity. Otherwise, none of the included covariates remained significant (Table 2). An exposure-effect model showed an independent effect of post-pandemic decline in the MoCA score, not affected by differences between subjects with history of mild symptomatic SARS-CoV-2 infection and their negative counterparts (average treatment effect: β = 0.24; 95% CI 0.07–0.41; p = 0.006).

Post-pandemic EEGs disclosed abnormalities in two individuals (both were SARS-CoV-2 seropositive and had cognitive decline). EEG abnormalities included left hemispheric slowing and sharp waves over the left temporal region in one subject (Figure 2) and right temporal lobe slowing in the other (Figure 3). Post-pandemic MRIs were normal in the 12 individuals with cognitive decline, including the two with abnormal EEGs.

TABLE 1 Characteristics of participants in this study across categories of SARS-CoV-2 serological status (univariate analyses)

Variable	Total series (n = 93)	SARS-CoV-2 negative (n = 41)	SARS-CoV-2 positive (n = 52)	p value
Age in years, mean ± SD	62.6 ± 11	66.6 ± 10.6	59.4 ± 10.6	0.002*
Female gender, n (%)	59 (63)	27 (66)	32 (62)	0.668
Body mass index ≥30 kg/m^2, n (%)	22 (24)	9 (22)	13 (25)	0.731
Blood pressure ≥140/90 mmHg, n (%)	30 (32)	18 (44)	12 (23)	0.033*
Fasting glucose ≥126 mg/dl, n (%)	25 (27)	10 (24)	15 (29)	0.631
Poor sleep quality, n (%)	32 (34)	11 (27)	21 (40)	0.172
Symptoms of depression, n (%)	9 (10)	4 (10)	5 (10)	0.982
Cognitive decline, n (%)	12 (13)	1 (2)	11 (21)	0.010*

*Statistically significant result.

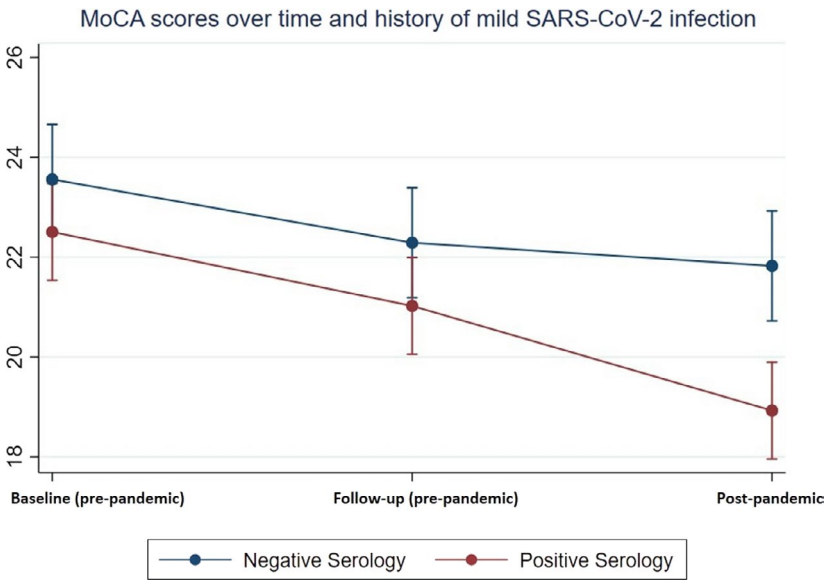

FIGURE 1 Graph showing changes in the Montreal Cognitive Assessment (MoCA) score over time according to history of mild symptomatic SARS-CoV-2 infection. MoCA scores were similar across categories of individuals in the baseline and follow-up pre-pandemic MoCAs but differ in the post-pandemic MoCA (no overlapping 95% confidence intervals), with a significant reduction among patients with history of mild SARS-CoV-2 infection [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Fully adjusted logistic regression model showing the independent association between history of mild symptomatic SARS-CoV-2 infection and cognitive decline (dependent variable)

Significant cognitive decline	Odds ratio	95% CI	*p* value
SARS-CoV-2 seropositivity	18.1	1.75–188	0.015*
Age	1.05	0.98–1.13	0.157
Female gender	0.52	0.13–2.08	0.357
Body mass index ≥30 kg/m^2	0.69	0.09–5.46	0.731
Blood pressure ≥140/90 mmHg	0.77	0.13–1.71	0.776
Fasting glucose ≥126 mg/dl	0.27	0.04–1.71	0.165
Poor sleep quality	2.89	0.55–9.57	0.257

Note: Symptoms of depression were not included in the model because of collinearity with cognitive decline.

Abbreviation: CI, confidence interval.

*Statistically significant result.

DISCUSSION

This prospective cohort study demonstrates that individuals with a history of mild symptomatic SARS-CoV-2 infections have more than 18 times the odds of developing cognitive decline than those without clinical and serological evidence of the infection. Such decline, however, remained mostly unnoticed by the majority of affected individuals and their family members. The predominantly subclinical cognitive decline detected after mild symptomatic SARS-CoV-2 infections may have long-term implications. It is important to characterize these changes in the sub-acute period to better understand the time course of progression or potential reversibility of cognitive changes after COVID-19.

As previously mentioned, no single study has prospectively evaluated changes in cognitive performance before and after the start of the SARS-CoV-2 pandemic in community dwellers according to whether they were infected or not by the virus. Therefore, our results are not comparable to previous studies. Nevertheless, some information can be extracted from published editorial comments that anticipate a potential increase in the prevalence of neurodegenerative disorders of the central nervous system among COVID-19 survivors [14–16]. A recent viewpoint article argued that patients with COVID-19 have increased risk of developing cognitive decline, which could be related to a delayed consequence of systemic inflammation occurring during the acute phase of the disease [16]. However, patients reported in the present study did not have a severe illness during acute disease, and differed from those who develop encephalitis, encephalopathy or a cytokine storm syndrome early in the course of infection. Most of the latter had already been admitted to intensive care units with severe respiratory distress at the time when they developed seizures or altered mental status [1–5]. Different phenotypes of disease expression probably result from diverse pathogenetic mechanisms accounting for the two conditions.

Neurotropism of SARS-CoV-2 may be the cause of delayed neurodegenerative diseases in patients with COVID-19 [34]. While the portal of entry of SARS-CoV-2 to the central nervous system is most often from the nasal olfactory epithelium to the olfactory bulb, the spread of the virus by trans-synaptic transfer to limbic structures and subsequently to deeper parts of the brain may explain the development of diffuse neurological manifestations. This has been demonstrated by positron emission tomography computed tomography showing abnormal fluorine-18 fluorodeoxyglucose uptake (hypometabolism) in limbic structures, frontal and orbito-frontal cortex, the cingulate gyrus and the thalamus/hypothalamus among COVID-19 survivors [35]. According to others, such abnormalities in brain metabolism may be related to inflammatory or autoimmune-related mechanisms, at least when those events were evident during the acute phase of the disease [36].

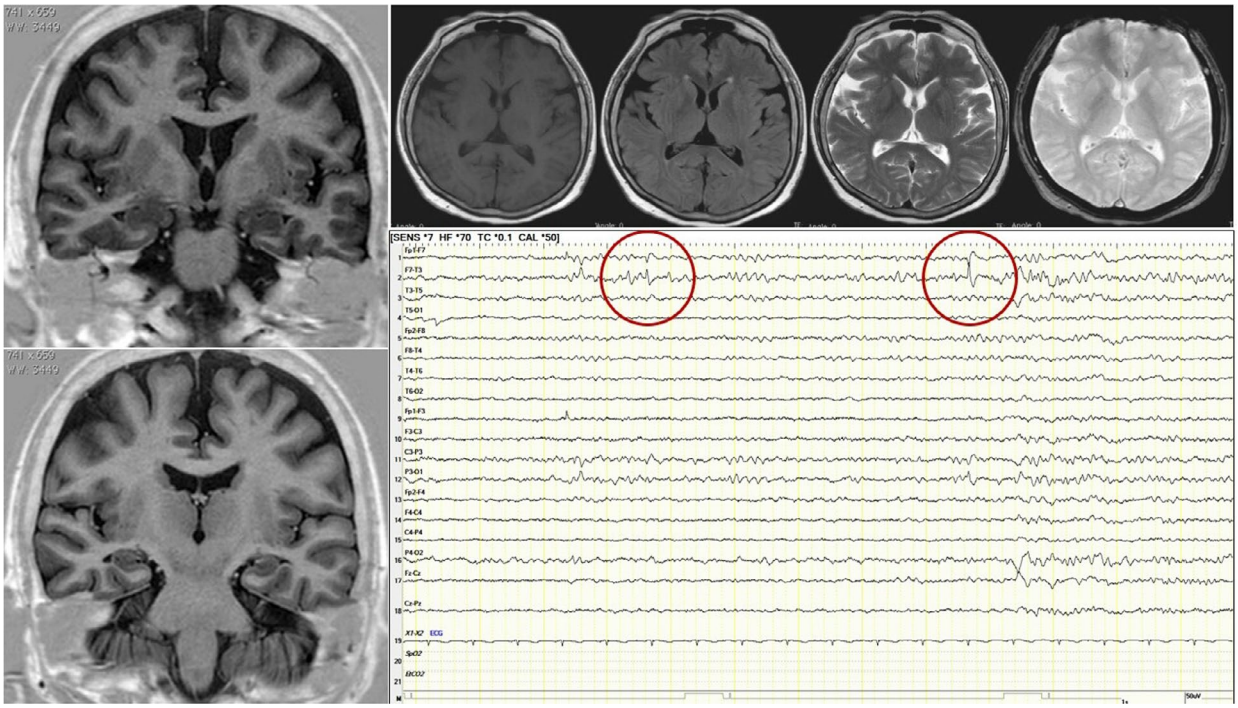

FIGURE 2 Post-pandemic MRI and EEG recording in a 58-year-old woman with cognitive decline. MRI is normal and the EEG shows left hemispheric slowing and sharp waves in the left temporal region (red circles) [Colour figure can be viewed at wileyonlinelibrary.com]

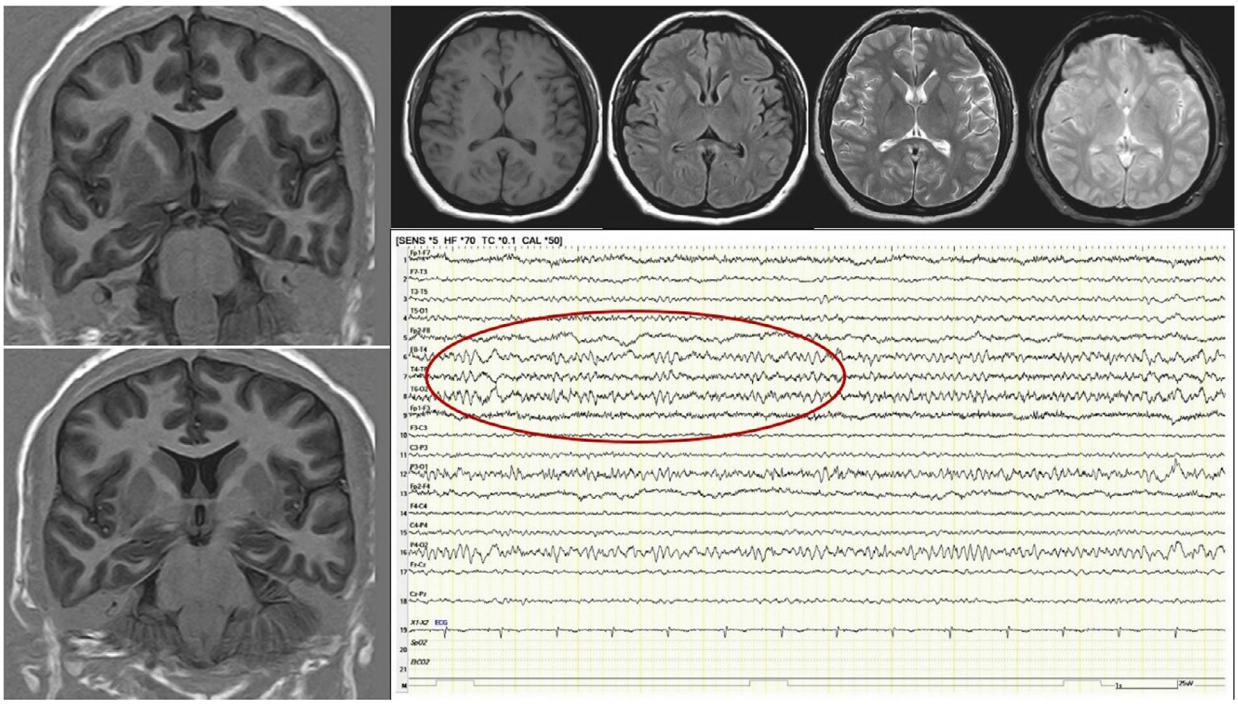

FIGURE 3 Post-pandemic MRI and EEG recording in a 44-year-old woman with cognitive decline. MRI is normal and the EEG shows right temporal lobe slowing (red circle) [Colour figure can be viewed at wileyonlinelibrary.com]

Several inflammatory biomarkers in the cerebrospinal fluid (CSF) were found in a small series of cancer patients with COVID-19-related encephalopathy developing 3 weeks after disease onset; however, none of them had detectable levels of SARS-CoV-2 by reverse transcriptase polymerase chain reaction in CSF [37]. A similar cytokine-mediated inflammatory response has been found in other conditions such as the immune effector cell-associated neurotoxicity syndrome, providing grounds for supporting the role of neuroinflammation in the pathogenesis of SARS-CoV-2-related cognitive decline [38].

In our patients, cognitive decline could be related to a delayed effect of the virus on the nervous system, since they did not disclose respiratory distress, acute encephalitis or any evidence of the cytokine storm syndrome during the acute phase of the disease. On the other hand, it is also possible that a more larvate and paucisymptomatic initial inflammatory response could express several months after the acute infection leading to a dysregulated immune response, which in turn may lead to chronic cognitive decline [4]. Pathogenetic mechanisms involved in the occurrence of neurological complications of SARS-CoV-2 infections are still under debate. Data from the present study do not allow definitive conclusions to be made on mechanisms involved in the pathogenesis of cognitive decline.

Several reports have focused on the development of EEG abnormalities in patients with SARS-CoV-2 infection during the acute phase of the disease [39–43]. The most common findings included rhythmic delta waves in the frontal lobes, disorganization of background activity, and epileptiform discharges. These abnormalities are often correlated with disease severity but are not specific to SARS-CoV-2 infection. In the present study, EEG recordings disclosed abnormalities in two (18%) of the SARS-CoV-2 infected individuals with cognitive decline, which were basically unilateral and included slowing of background activity and sporadic sharp waves. However, in view of the possibility that a 1-h scalp EEG recording may miss intermittent abnormalities, the actual prevalence and type of abnormalities found in the EEG of patients with SARS-CoV-2-related cognitive decline cannot be determined. On the other hand, the normality of brain MRIs in these cases eliminated the possibility of brain oedema, vascular lesions, hippocampal atrophy or any other macroscopic structural changes.

The longitudinal prospective design, together with the systematic evaluation of participants before and several months after the start of the SARS-CoV-2 pandemic, the stringent inclusion criteria and the fact that individuals with recent infections were excluded from analysis, are major strengths of the present study. The relatively small sample size is a potential limitation. However, the high endemicity of SARS-CoV-2 infection in the entire population of middle-aged and older adults living in Atahualpa (52.4%) is similar to that in the subset of seropositive individuals enrolled in the present study (56%), arguing for the representativeness of the current sample. Moreover, the robust significance in the multivariate model attempting to find an association between the main variables of interest, as well as the power analysis, are indicators of a satisfactorily powered sample. Also, it cannot be excluded that some patients without cognitive decline will develop this complication in the future, making the above-described relationship even more evident. On the other hand, longer-term follow-up in the same cohort may demonstrate that cognitive performance returns to baseline levels in those with a current cognitive decline.

The study population was limited to people aged ≥40 years. As such, cases of cognitive decline among younger individuals with SARS-CoV-2 infection were missed. CSF analysis was not performed in patients with a positive outcome and, although the virus is not often detectable in the CSF, measurement of cytokines would have been of interest from a pathogenetic perspective [37,44]. While the test used for SARS-CoV-2 diagnosis is reported to be highly reliable, a small degree of misclassifications due to false positive or false negative results [45] or the remote possibility of cross-reactions with other viruses that are endemic in the region [46] cannot be ruled out. In addition, a single test was relied on to assess cognitive performance. While the MoCA is limited compared to neuro-psychological testing batteries, it has been validated in differentiating mild cognitive impairment from Alzheimer's dementia and has a correction for low education levels. In addition, the MoCA has proven reliable for assessing cognitive performance and correlated well with structural brain damage in the study population [47]. Another limitation of the study, inherent to the EEG itself, is that scalp EEG recordings may miss an infrequent epileptiform activity or focal slowing [48]. Therefore, it is possible that abnormalities found in the post-pandemic EEGs were also present, but not captured, by pre-pandemic recordings.

CONCLUSION

This study is the first to demonstrate cognitive decline among individuals with a history of mild symptomatic SARS-CoV-2 infection, providing evidence of the existence of this complication. The persistence of SARS-CoV-2 in the central nervous system may be responsible for this complication, but other pathogenetic mechanisms may account for its occurrence. The organization of post-COVID-19 outpatient clinics will be of value to better understand correlates and mechanisms that are in the path of delayed complications of SARS-CoV-2 infection, not only at the neurological level but also those chronically affecting the respiratory and cardiovascular systems [49]. Further studies are needed to replicate our findings and to get more insights on the pathogenesis of cognitive decline among COVID-19 survivors. Intervention strategies may then be planned to improve the health and mental status of people with a history of COVID-19.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Oscar H Del Brutto: Conceptualization (lead); supervision (lead); writing original draft (lead). Shasha Wu: Investigation (equal); writing original draft (supporting). Robertino M Mera: Formal analysis (lead). Aldo F Costa: Data curation (lead); investigation (equal). Bettsy Y Recalde: Data curation (supporting); investigation (supporting); supervision (supporting). Naoum P. Issa: Data curation (equal); investigation (supporting); writing review and editing (supporting).

DATA AVAILABILITY STATEMENT

Data will be shared upon reasonable request to the corresponding author.

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