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Executive dysfunctions in patients recovering from Covid-19

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Abstract

COVID-19 is recognized as a multi-organ disease that can affect many organs either during the acute stage of infection or even after recovery. These are part of the post COVID-19 syndrome. Neuropsychiatric symptoms such as cognitive impairments are part of them and include memory difficulties, executive functions impairments, and trouble focusing. However cognitive profile in these patients is still not precise and underlying mechanisms are still unclear. Besides, most studies were performed in western or Asian countries. Almost no studies were performed in African or Arab countries. The aim of our study was to assess neuropsychiatric and cognitive disorders in Tunisian patients who recovered from Covid-19 A cross-sectional survey was conducted during the months of May and June 2021, including patients one month after discharge from the pneumology ward in Mongi Slim Hospital in Marsa Tunisia. They all were hospitalized there for COVID-19 infection. Socio-demographic and clinical data were collected from medical records and through interviewing patients directly. To assess cognitive impairment, we used: Mini Mental State (MMS), Frontal Assessment Battery (FAB), Trail Making Test (TMT), and the maze task. Anxiety and depressive symptoms were also screened using the Hospital Anxiety and Depression. Twenty patients were included in the study, with 65% males. There were 14 patients with at least one cognitive dysfunction, which represents 70% of the sample. Three patients had less than the cut off score on the MMS and 8 patients on the FAB (showing respectively memory and executive impairment). On the TMT and the maze task, respectively 5 and 9 patients had abnormal timing scores. Patients hospitalized with COVID-19 may show cognitive impairment shortly after discharge. Memory and executive functions are the most affected domains. For better management of these patients, screening for cognitive disorders in post COVID is vividly recommended. Long term studies are needed to check whether these impairments remain after the early phase.

Keywords: *cognitive impairments, executive functions, psychiatric symptoms, long covid*

Introduction

SARS-CoV-2 is the novel coronavirus that first emerged from China in December 2019 and the seventh member of the coronavirus family [1]. The outbreak of this infection was officially named as Coronavirus Disease 2019 (COVID-19) by the World Health Organization [2]. With the help of numerous studies, it became possible to characterize this new infection, which we originally thought to manifest primarily with respiratory symptoms [3].

Now, Covid-19 is recognized as a multi-organ disease that can affect a large number of vital organs beyond the lungs, such as the heart, kidneys, and the brain during the acute infection [4]. On the other hand, it has been demonstrated that SARS-COV2 infection can lead to clinical remaining symptoms despite resolution of the acute infection [5]. COVID-19's approximate healing time is 2–3 weeks. Yet, 1 in 5

people might display symptoms for more than 5 weeks, while 1 in 10 may still suffer from residual symptoms after 12 weeks [2].

Asthenia, dyspnea, myalgia, joint pain, headache, persistent coughing, chest pain, altered smell and taste and diarrhea were the 10 most reported ones [2]. These are part of the post COVID-19 syndrome. Among these residual symptoms, studies suggested that neuropsychiatric symptoms such as cognitive impairments could affect some patients during SARS-COV2 recovery [6,7]. The neurocognitive symptoms associated with COVID-19 patients are becoming a highly studied area due to the increased frequency of reported cases. Among them, recent data shed light on memory difficulties, executive functions impairments, as well as trouble focusing. It is currently the fourth most reported long-term symptom after COVID-19 recovery [8]. Neurocognitive pathophysiology in COVID is complex. Among the hypotheses of recent data, direct neuronal damage, neuro-inflammation, microvasculitis and hypoxia could be the major factors involved in neuro-cognitive sequelae [9].

However, the cognitive profile of these patients remains unclear and requires further investigation to evaluate its impact and understand more precisely the underlying mechanisms [7]. Multiple hospital case series and observational studies were performed in western or Asian countries. However, African and Arab countries still lack information regarding this topic since little to no studies were carried out there.

The aim of our study was to assess neuro-psychiatric symptoms, and more specifically cognitive disorders, in Tunisian patients who recovered from Covid-19.

Methods

A cross-sectional survey was conducted during the months of May and June 2021.

The patients were selected from the pneumology ward in Mongi Slim Hospital in Marsa, Tunisia. We specifically chose patients who were hospitalized there due to Covid-19 infection and the study was conducted one month after discharge. Informed consent was obtained from all the included patients.

Socio-demographic and clinical data were collected from medical records and through interviewing patients directly. Multiple valid scales were used to assess cognitive impairment: Mini Mental State (MMS) [10], Frontal Assessment Battery (FAB) [11], Trail Making Test (TMT) [12], and the maze task [13]. Anxiety and depressive symptoms were also screened using the Hospital Anxiety and Depression (HAD) [14].

The MMS is a psychometric screening that assesses cognitive function. It explores various cognitive domains such as orientation, memory, attention, comprehension, expression, and praxis. It has the advantage of being widely used in outpatient follow-up to assess cognitive impairment over time [15].

The FAB is a short cognitive and behavioral battery used to assess the six domains of frontal lobe function: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control and environmental autonomy [11,16]. It thus consists of six subtests, each exploring one of the aforementioned executive functions. The total scores are obtained by adding the subscores of the six subtests [11]. This test assesses cognitive functions in general. Other tests, such as TMT and Mase Task are used to assess more accurately specific executive domains.

The TMT is a neuropsychological instrument that assesses the speed of cognitive processing and executive functioning. It consists of two parts: the TMT A and the TMT B. The TMT A measures visual search and motor speed, whereas the TMT B explores cognitive flexibility, divided attention and working memory (frontal executive functions). Each test involves a set of exercises that require patients connecting numbers and letters. The scoring of each part is determined via the time of completion of the tasks.

The Maze Task is a timed paper-and-pencil procedure that assesses spatial navigation, which depends on a large number of cognitive processes: visual perception, spatial orientation, learning, and memory. The task consists of tracing a path through 5 different mazes presented successively. The total score is measured via 3 variables: completion time, planning time, and errors/dead ends.

The HAD is a scale that assesses anxiety and depressive symptoms. It consists of 14 items: 7 depression items and 7 anxiety items that both focus on the cognitive and emotional aspects. Somatic items are excluded.

Statistical analysis was performed using the IBM SPSS Version 23.0 (IBM Inc) program. Correlation analysis was conducted with Pearson's and Spearman's analysis for parametric and nonparametric variables, respectively. Chi-square tests were used for qualitative variables. A p value < 0>

Results

The sample included 20 patients, with a sex ratio of 2 males/1 female. The patients' sample average age

was 63. The main COVID symptoms that were described were asthenia, myalgia, cough and fever.

Thirty percent were smokers. Mean Body Mass Index was 28 (range :21-36). Sixty percent had medical history of diabetes or high blood pressure and 20 percent had coronaropathy. Lesions extent on computed tomography (CT) scan was 45.5 with a range of 20 to 37. Oxygen flow had an average of 8.2 litres per minute with a range of 1 to 15.

Multiple complications were reported during the course of the hospitalization. In total, 12 patients suffered from bacterial infection and 2 patients presented an agitation episode. No cardiovascular complications were reported. Two patients were taken to the intensive care unit to receive noninvasive ventilation for a duration of 5 days and 10 days respectively.

Fourteen out of the 20 patients were diagnosed with at least one cognitive dysfunction, which represents 70% of the sample.

Memory and executive functions were evaluated using the MMS and the FAB. Three patients obtained less than the cut off score on the MMS. Eight patients had low scores on the FAB showing executive impairments.

Flexibility, attention and planning abilities were evaluated through the TMT and the Maze Task. On the TMT and Maze task tests, respectively 5 patients and 9 patients have abnormal timing scores. There were also mild rates of depression and anxiety. All cognitive and psychiatric mean score's tests are detailed in Table 1.

There was no statistical significant association between cognitive dysfunction and demographic or clinical parameters. There was no statistical association between depression, anxiety and cognitive impairment

Table 1. Patients scoring on executive measures and psychiatric scales

MMS	*25.75 (min: 10; max: 30)*
FAB	*14.65 (min: 8 max: 18)*
TMT-A duration	*133.53 seconds (min: 20; max: 309)*
TMT-B duration	*217.11 seconds (min: 41; max: 340)*
MAZE task duration	*59 seconds (min: 7; max: 139)*
HAD anxiety	*8 (min: 0; max: 18)*
HAD depression	*6.6 (min: 2; max: 14)*

Discussion

This study found cognitive impairments in Tunisian patients after COVID-19 hospitalization. In our study, 70% of the sample had cognitive dysfunctions. Several cognitive executive domains were affected such as flexibility, speed processing, attention and planning functions.

Hampshire et al. found that COVID-19 could significantly impact various cognitive abilities [17]. Zhou et al reported that the cognitive impairments in COVID-19 patients were mild [18]. They mostly affected sustained attention, and were correlated with C-Reactive Protein level which is a marker of inflammation [10]. A recent meta-analysis found that COVID-19 affected executive functions, attention, and memory [6]. Cognitive symptoms are more prevalent in patients with severe infection who needed hospitalization.

In this study, anxiety and depression were not associated with cognitive impairments.

We still lack understanding about the physiological mechanisms that could induce long lasting impairments after COVID-19 recovery. Though, literature mentions several factors that could be involved in the pathogenesis of cognitive impairments in COVID-19.

Among these factors, systemic inflammation, which consequently leads to neuro-inflamation, is the most listed one [19]. This chronic inflammation was widely studied to help figure out how it impacts cognitive functions.

Multiple studies suggest that SARS-CoV-2 virus may access to the central nervous system through the nasal mucosa and olfactory fibers, or by the haematogenous path [7].

Once SARS-Cov-2 enters the central nervous system, it's by infecting endothelial cells, pericytes and probably neurons that it causes cascading reactions that end up altering cognitive functions [7].

Moreover, animal models showed that memory impairment could be explained by the vulnerability of hippocampus to respiratory viral infections [20]. In fact, Areza-fegyveres et al suggested that hypoxia could account for cognitive impairments in several coronaviruses' infections [21]. There is increasing supporting evidence that cerebral hypoperfusion accelerates amyloid-beta accumulation in the brain, which further explains cognitive dysfunction since Alzheimer's pathophysiology implies amyloid-Beta accretion [7].

Actually, COVID-19 has been closely linked to cognitive impairments in neuro-degenerative diseases including Alzheimer's [22]. Cerebral white matter is particularly vulnerable to ischemic damage in COVID-19 and plays a big role in cognitive function.

However, cognitive impairments following COVID-19 infection seem to have some atypical features: they may last longer, affect younger people and associate affective symptoms [23].

In the literature, intensive care unit admission and the use of invasive treatments like ventilation and sedation are risk factors of cognitive decline [21]. Our sample was not representative enough with only 2 patients requiring intensive care units admission and invasive treatment. Both did not present any significant cognitive impairment.

This study is original because it is the first study in an African country however the sample size and the absence of a control group were the 2 main limitations of this study. The main reason was the rapid widespread of the virus and that most people could have asymptomatic infections. Hence it is was not possible to recruit a control group who was never infected.

Conclusion

Patients hospitalized with COVID-19 can develop cognitive impairments shortly after discharge, especially in case of severe infection. Memory and executive functions are the most affected domains.

This pilot study could be the starting point of more extensive researches regarding COVID-19 induced cognitive impairments especially in African and Arab countries. Screening for cognitive disorders in post-COVID is crucial can be performed using paper and pencil-based tests for wider use in developing countries.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Authors have no conflicts of interest

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