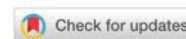


COGNITIVE IMPAIRMENTS AS A SYMPTOM OF POST-COVID SYNDROME AMONG THE BULGARIAN POPULATION IN THE CONTEXT OF A GLOBAL PANDEMIC: AN ONGOING STUDY

Miroslava Hristova^{1*}, Radka Massaldjieva²

¹UMHAT "St. George", Plovdiv, Clinic of Neurology, Bulgaria, e-mail: miroslava.mgh@gmail.com

²Medical University of Plovdiv, Faculty of Public Health, Department of Health Care Management, Bulgaria
e-mail: radka.massaldjieva@mu-plovdiv.bg



Abstract: Isolated in China at the end of 2019, the novel Corona virus - SARS-CoV 2 spread worldwide with remarkable speed, causing a state of global health emergency just a few months later. And yet as we passed the acute phase of the COVID 19 pandemics, healthcare workers face the challenge of its late consequences. Therefore, the World Health Organization defined a new condition - post-COVID syndrome (PCS, Post-acute COVID Syndrome or long-COVID). According to several studies, the incidence of PCS varies from 10% to 35% among non-hospitalized patients and up to 85% among hospitalized patients. Moreover, various study results show that the syndrome affects both patients with a symptomatic form of the infection and those with an asymptomatic course. The syndrome itself presents with a wide range of non-specific complaints, most frequent of which are fatigue, shortness of breath and impaired cognitive functions. The exact pathogenetic mechanisms, responsible for these prolonged neuropsychological manifestations of long COVID 19 are yet to be established but most authors assume that they are caused by chronic neuroinflammation.

Purpose: The aim of our study is to assess the most common cognitive impairments among the Bulgarian population, thus providing information about their characteristics and incidence.

Methods and materials: We conducted a prospective study among 75 patients, all of which have recovered from COVID 19 infection at least 3 months prior to testing. All participants were between 20 and 60 years old and had no previous neurological or psychiatric disease. To assess cognitive functions, we used a computer test - the Cogstate Brief Battery, which provides a measure of four core cognitive domains: processing speed, attention, visual learning and working memory.

Results: The study is still ongoing, as we intend to conduct a follow-up testing on the sixth month. So far, our results are in accordance with findings in other countries, showing that executive functions and memory are predominantly affected. Therefore, it is important to underline the fact that there are objective findings for the non-specific subjective complaints.

Conclusion: Outlining the possible clinical features of long-COVID and emphasizing its undeniable medico-social meaning is of undeniable importance to healthcare workers. And given the progressively rising morbidity from this novel syndrome, a more precise description of these "cognitive impairments" is required in order to formulate epidemiologically based health strategies and ensure early prevention, especially in patients in an active age.

Keywords: cognitive functions, cognitive impairments, post – COVID syndrome, neuropsychological test, COVID 19
Field: Medical sciences and Health

INTRODUCTION

At the end of 2019 a new virus (SARS-CoV-2) was isolated in the city of Wuhan, China, when it caused a series of cases of severe pneumonia, resistant to the current therapies. In March of 2020 the World Health Organization (WHO) declared a COVID 19 pandemic. According to the official WHO statistics, based on laboratory-confirmed cases, the pandemic has affected more than 765 million people globally, while the reported casualties are estimated to be a little less than 7 million deaths globally. Many mathematical models, however, suggest that the real number of infected people is approximately 10 times greater than the official data (from 3 to 24 times). 1,2

However, the average duration of the acute phase of COVID 19 infection is between 1 and 4 weeks. So, with the progression of time, the number of recovered patients is increasing and many of them are reporting a wide range of persistent complaints. In 2021 a large-scale study (REACT-2) was conducted in the United Kingdom 4 to determine the incidence of 29 persistent post-COVID complaints among 508,707 recovered patients. The results showed that 37.7% of the participants reported having one or more

*Corresponding author: miroslava.mgh@gmail.com



residual symptoms, with only a third of them having experienced a severe COVID-19 infection. According to the prospective follow-up study of Logue et al. (2021) 5 about 30% of those affected by COVID 19 reported residual symptoms such as fatigue, headache, impaired memory, difficult concentration, hypo/anosmia and impaired taste, depression and anxiety. According to another study by Woo et al. (2020) 78% of those, who have recovered from a mild or moderately severe form of COVID 19, experience cognitive difficulties. In 2021 Graham et al. 7 conducted a prospective study among the first 100 patients of a Neuro-COVID clinic in the USA. They found that the most common symptoms, persisting for more than 6 weeks are: "brain fog" (81%), headache (68%), paresthesia (60%), impaired taste (59%), anosmia (55%) and muscle aches (55%). These results prove that medical professionals are already facing the challenges of this new postacute condition and its impact on everyday life and professional functioning.

Thus, the WHO defined a new condition – post acute COVID syndrome (PACS) or long-COVID. According to the official definition, PACS is a condition that occurs in people with laboratory-proven or probable COVID 19 infection and is established at least 3 months after the initial infection. The syndrome includes new or residual symptoms that persist for at least another 2 months and cannot be explained by another diagnosis. The most frequent complaints are fatigue, shortness of breath and cognitive dysfunction, with yet no proven correlation between the severity of the initial infection and the likelihood of developing post-COVID syndrome. correlation between the severity of the initial infection and the likelihood of developing post-COVID syndrome.

The first studies, trying to determine the specifics of the cognitive impairments as a symptom of PACS, were conducted in some of the most affected countries. In 2021, in the USA, Frontera et al. (2021) 6 selected a group of 382 hospitalized SARS-CoV-2 positive patients, aged between 55 and 77 years. Some of them (196/382) had neurological symptoms during the acute phase of the disease, while others were treated at an intensive care unit. After discharge, patients were followed-up at the 6th month using the the Montreal Cognitive Assessment (MoCA) and Barthel Index (BI - to assess the ability to cope with daily activities). Of all examined, 50% showed cognitive impairments and MoCA results below 18 points, and 44% experienced difficulties in performing some daily tasks. Similar are the results obtained by Walle-Hansen et al. (2021.) 7 who also used the MoCA to assess the cognitive functions in a group of 106 patients. Six months after hospitalization, 43% of them showed impaired cognition. Lamontagne et al. (2021)8 conducted a study, including 50 healthy controls and 50 patients who had recovered from COVID 19 infection and had no previous evidence of neuropsychiatric complaints. The authors used a computer test to assess executive functions, orientation and active attention (ANT - Attention Network Test). The final analysis showed that cognitive impairments were most pronounced during the first 1 to 4 months after the acute infection, with executive functions and memory being predominantly affected, while orientation and active attention were relatively intact. These data correlate with the changes in brain glucose metabolism found by Blazhenets et al. (2021) 9. The authors followed-up a small cohort of 8 patients using 18F-FDG PET and neuropsychological assessment (MoCA) – once during the subacute phase and again approximately 6 months after the initial diagnosis. The results of the first 18F-FDG PET showed neocortical glucose hypometabolism, predominantly in the frontoparietal and, to a lesser extent, in the temporal regions. These results were corresponding to lower MoCA results. Re-examination in the chronic phase of COVID 19 revealed an improvement in cognitive function and MoCA scores, accompanied by a significant reduction in neocortical glucose hypometabolism, but without full recovery. One possible hypothesis is that this residual glucose hypometabolism is secondary to other pathohistological changes of the brain parenchyma.

There is still no consensus on the exact pathogenetic mechanisms by which the SARS-CoV-2 virus causes persistent symptoms. There are a few hypotheses, but most authors accept that SARS-CoV-2 may induce persistent inflammation in the body, which can possibly have a central role in the pathogenesis of PACS. Chronic inflammation is also associated with increased plasma levels of pro-inflammatory cytokines (IL-1, IL-6, IL-10, TNF- α). The latter disrupt the permeability of the blood-brain barrier, pass into the Central nervous system (CNS) and activate microglial cells. In general microglia have anti-inflammatory functions and promote recovery processes. However, their prolonged activation leads to alteration, abnormal proliferation and induction of pro-apoptotic processes, as well as in situ synthesis of inflammatory cytokines and factors, promoting neurodegeneration. This way the impaired permeability of the blood-brain barrier and the high levels of cytokines in the CNS and plasma, potentiate each other and thus support the process of neuroinflammation in the CNS. Prolonged microglial activation leads to subsequent disruption of neuroplasticity, synaptic function, and myelination. This chronic neuroinflammation is very similar to that in some other chronic diseases of CNS like Alzheimer's disease. (Da browska et al. 2021; Kempuraj et al. 2020; Stefano et al. 2021; Proal et al. 2021, Pacheco-Herrero et al. 2021; Robinson-Agramonte et al. 2021, Robeiro et al. 2020; Borah et al. 2021, Sun et al. 2021 –

10,11,12,13,14,15,16,17,18).

MATERIALS AND METHODS

The aim of our study is to determine the most common cognitive impairments among the Bulgarian population, thus providing information about their characteristics and incidence. For this purpose, we selected a group of 75 patients (to date) 75 patients, all of which have recovered from COVID 19 infection at least 3 months prior to testing. All participants are between 20 and 60 years old and have no medical history of previous neurological or/and psychiatric disease, cancer or substance abuse. Patients who were reinfected with SARS-CoV 2 between the initial testing and the follow-up were excluded. All participants signed a consent form.

In order to assess cognitive functions, we used a computer test - the Cogstate Brief Battery, which provides a measure of four core cognitive domains: processing speed, attention, visual learning and working memory. All tests are conducted under the supervision of a member of the research team. The test was performed on a laptop. This CogState battery (CAB) included several subtests:

- Continuous Paired Associate Learning (CPAL - "In what locations do these pictures belong?") – measures delayed visual memory through paired associate learning. Administration time for healthy participants is 7 minutes.
- Groton Maze timed chase test (GMCT)- measures speed of visual processing.
- Groton Maze learning test (GML) – to assess executive function. Administration time for healthy participants is 7 minutes.
- One-card learning (OCL - "Have you seen this card before?") and One-back memory (ONB – "Is the previous card the same?") - measures working memory. Administration time for healthy participants is respectively 6 and 4 minutes.
- Identification test ("Is the card red?") – to assess attention. Administration time for healthy participants is 4 minutes.

All participants will perform the same test on a follow-up meeting 6 months after the first testing.

RESULTS

Since our study is still ongoing, we intend to include at least 25 more patients before the final analysis. To date however we do notice slight deficits in the tests, assessing executive functions, speed of visual processing and working memories. Most of the participants who are confident at the beginning show unsatisfiable speed in performing the subtests and a noticeable number of mistakes. These deficits are more pronounced in patients with a more recent COVID 19 infection, despite the lack of subjective complaints in many cases.

DISCUSSION

Most of the studies, evaluating cognitive functions as a symptom of long COVID, are being conducted in the countries, affected most by the pandemic (China, Great Britain, USA, Italy). Although there are still many unanswered questions, the studies to date provide useful information about the specifics of the observed cognitive impairments, revealing a predominant involvement of executive functions and memory. The published results prove that the subjective complaints of "brain fog" and impaired concentration are associated with objective findings, giving invaluable guidance to clinicians to look for specific deviations in cognitive functions when examining recovering patients. Regarding pathogenesis, the role of neuroinflammation and glucose hypometabolism is emphasized, which expands potential possibilities for prevention and treatment.

CONCLUSION

The results of these studies give us a clearer clinical and diagnostic picture of a new syndrome, allowing the scientific and medical community to apply a more targeted approach in dealing with this new challenge. This data is useful especially for small countries, where a timely screening for cognitive disorders at the beginning of the chronic, or even in the subacute phase of the infection, would allow early

treatment and limit the potential health and economical consequences for the population.

Acknowledgements

This work was supported by Medical University of Plovdiv under project № ДПДП-12/2022.

REFERENCES

- Coronavirus disease (COVID-19) – World Health Organization. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>, посетен януари 2022г.
- COVID-19. World Health Statistics. Geneva: World Health Organization; (<https://www.who.int/data/gho/publications/world-health-statistics>, посетен септември 2022г.
- Varatharaj A., Ellul M., Davies N. et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *Lancet Psycairy* 2020; 7:875-82; Published online June 25, 2020, [https://doi.org/10.1016/S2215-0366\(20\)30287-X](https://doi.org/10.1016/S2215-0366(20)30287-X)
- Whitaker M, Elliott J, Chadeau-Hyam M. et al. Persistent symptoms following SARS-CoV-2 infection in a random community sample of 508,707 people. *medRxiv*. 2021 <https://doi.org/10.1101/2021.06.28.21259452> p. 2021.06.28.21259452.
- Logue, J.K., Franko, N.M. McCulloch et al, 2021. Sequelae in adults at 6 months after COVID-19 infection. *JAMA Netw Open*. 4 (2), e210830. <https://doi.org/10.1001/jamanetworkopen.2021.0830>.
- Frontera, J.A., Yang, D., Lewis, A., et al, 2021. A prospective study of long-term outcomes among hospitalized COVID-19 patients with and without neurological complications. *J. Neurol. Sci.* 426, 117486. <https://doi.org/10.1016/j.jns.2021.117486>.
- Walle-Hansen, M.M., Ranhoff, A.H., Mellingsæter, M. et al, 2021. Health-related quality of life, functional decline, and long-term mortality in older patients following hospitalisation due to COVID-19. *BMC Geriatr.* 21 (1), 199. <https://doi.org/10.1186/s12877-021-02140-x>.
- Steven J. Lamontagne, Makaila F. Winters, Diego A. Pizzagalli, et al. Post-acute sequelae of COVID-19: Evidence of mood & cognitive impairment, *Brain, Behavior, & Immunity - Health*, Volume 17, 2021, 100347, SSN 2666-3546, <https://doi.org/10.1016/j.bbih.2021.100347>.
- Ganna Blazhenets, Nils Schroeter, Tobias Bormann, et al. Slow but Evident Recovery from Neocortical Dysfunction and Cognitive Impairment in a Series of Chronic COVID-19 Patients; *Journal of Nuclear Medicine* Jul 2021, 62 (7) 910-915; DOI: 10.2967/jnumed.121.262128
- Dabrowska E., Galinska-Skok G., Waszkiewicz N., Depressive and Neurocognitive Disorders in the Context of the Inflammatory Background of COVID-19. *Life* 2021, 11, 1056, <https://doi.org/10.3390/life11101056>
- Proal A. and VanElzakker M. et al, 2021. Long COVID or Post-acute Sequelae of COVID-19 (PACS): An Overview of Biological Factors That May Contribute to Persistent Symptoms. *Frontiers in Microbiology*, June 2021, Volume 12, Article 698169, doi: 10.3389/fmicb.2021.698169
- Kempuraj D., Selvakumar G., Ejaz Ahmed M., et al. COVID-19, Mast cells, Cytokine storm, Psychological Stress and Neuroinflammation. *The Neuroscientist* 2020, Vol. 26(5-6) 402–41
- Stefano G., Buttiker P., Weissenberger S. et al.; Editorial: The Pathogenesis of Long-Term Neuropsychiatric COVID-19 and the Role of Microglia, Mitochondria, and Persistent Neuroinflammation: A Hypothesis. e-ISSN 1643-3750 © Med Sci Monit, 2021; 27: e933015 DOI: 10.12659/MSM.933015
- Pacheco-Herrero M., Soto-Rojas L., Harrington C., et al, (2021). Elucidating the Neuropathologic Mechanisms of SARS-CoV-2 Infection. *Front. Neurol.* 12:660087. doi: 10.3389/fneur.2021.660087
- Ribeiro D., Oliveira-Giacomelli A., Glaser T., et al. Hyperactivation of P2X7 receptors as a Culprit of COVID-19 Neuropathology. *Molecular Psychiatry*, 2020. <https://doi.org/10.1038/s41380-020-00965-3>
- Borah P., Deb P., Chandrasekaran B., et al, 2021. Neurological Consequences of SARS- CoV-2 Infection and Concurrence of Treatment-Induced Neuropsychiatric Adverse Events in COVID-19 Patients: Navigating the Uncharted. *Front. Mol. Biosci.* 8:627723. doi: 10.3389/fmolb.2021.627723
- Robinson-Agramonte M., Gonçalves C., Noris-García E., et al. Impact of SARS-CoV-2 on neuropsychiatric disorders. *World J Psychiatr* 2021; 11(7): 347-354
- Sun, B.; Tang, N.; Peluso, M. J. et al. Characterization and Biomarker Analyses of Post-COVID-19 Complications and Neurological Manifestations. *Cells* 2021, 10, 386. <https://doi.org/10.3390/cells10020386>