p-ISSN: 2184-2205 e-ISSN: 2184-3414 ISBN: 978-989-35106-6-7 © 2024

# COGNITIVE FUNCTIONS IN A SERIES OF PATIENTS AFTER ACUTE COVID 19 INFECTION – CASE SERIES

**Miroslava Hristova[1,3], Radka Massaldjieva[2], Lyubomir Chervenkov[4], & Penka Atanassova[1,3]**

*[1]UMHAT "St. George", Plovdiv, Neurology Clinic, Bul. Peshtersko shose 66, Plovdiv 4002 (Bulgaria)*
*[2]Medical University of Plovdiv, Faculty of Public Health, Department of Health Care Management, Bul. Vasil Aprilov 15A, Plovdiv 4002 (Bulgaria)*
*[3]Medical University of Plovdiv, Faculty of Medicine, Department of Neurology, Bul. Vasil Aprilov 15A, Plovdiv 4002 (Bulgaria)*
*[4]Research Complex for Translational Neuroscience, Medical University of Plovdiv, Bul. Vasil Aprilov 15A, Plovdiv 4002 (Bulgaria)*

## Abstract

The exact number of COVID-19 cases worldwide is unknown – it is estimated that the real number of cases is much greater than the laboratory-confirmed, positive patients. A large part of these patients, up to 85% according so some studies, present at a later stage with persisting heterogenous non-specific symptoms, defined by the World Health Organization (WHO) as Post-acute COVID syndrome (PACS, long-COVID or Post-COVID syndrome). Among the myriad manifestations of PACS, the most common are shortness of breath, fatigue, and cognitive dysfunction including impaired concentration and forgetfulness, all of which are negatively influencing the quality of life of patients. There is still no unanimous consensus, regarding the exact pathogenetic mechanisms of the long-term post-COVID manifestations and no established guidelines for their treatment. Therefore, it is necessary to continue the in-depth study of PACS and its cognitive symptoms. We studied 68 subjects with post-acute COVID syndrome (PACS) – using a detailed clinical interview, a non-contrast magnetic resonance imaging (MRI) brain scan and a computer-based neuro-psychological test - the CogState Brief Battery, assessing four core cognitive domains: processing speed, attention, visual learning and working memory. Our aim here is to present a case series of 4 subjects, in early and middle adulthood who have recovered from a mild COVID 19 infection in the previous year, and which showed hippocampal enlarged perivascular space (H-EPVS) on MRI. The analysis of the acquired test results showed that all subjects had lower (> 53%) than expected accuracy in one subtest of the CogState Brief Battery, compared to healthy individuals. Two of the participants performed worse on the same CogState subtest at follow-up on both outcome measures, compared to baseline. These results confirm the need for objective examination and follow-up of patients with subjective cognitive complaints with sensitive neuropsychological methods and neuroimaging.

***Keywords:*** *Cognitive functions, computer-based neuropsychological test, post-COVID syndrome.*

## 1. Introduction

It is difficult to determine the exact number of COVID-19 cases worldwide. Some statistical models suggest that the real number of infected individuals is approximately 10 times greater that the laboratory-confirmed cases. And many of those who have recovered from the acute COVID 19 infection experience a condition, defined by WHO as post-COVID syndrome.

There is already a large amount of literature data on the connection between a prior SARS-CoV-2 infection and persistent cognitive problems (Altuna et al., 2021). According to Woo et al. (2020), 78% of those, who have recovered from a mild or moderately severe form of COVID 19, experience cognitive difficulties. Walle-Hansen et al. (2021) conducted a study, using Montreal Cognitive Assessment (MoCA), and established that 43% of them showed impaired cognition 6 months after COVID 19 infection. The risk for cognitive impairments is higher for patients after severe infection, but cognitive complaints and objectively found cognitive decline that follow the mild SARS-CoV-2 infection are now a scientific challenge more so as they often affect young patients and their everyday life. (Altuna

et al., 2021; Ceban et al., 2022). In a recent meta-analysis of 81 studies an international team of researchers tried to analyse the data about the prevalence of cognitive impairments a year after COVID-19 diagnosis and found a significant proportion of 0,22, greater for females. They found as well that cognitive problems are long-term, with no difference between the patients followed up at the 6th month and those followed up a year later (Ceban et al., 2022).

So far, no unanimous consensus has been reached either on possible treatment, or on the mechanisms by which the infection provokes the long-term negative manifestations, although many authors discuss the central role of immune dysregulation, chronic neuroinflammation and possible neurodegeneration. Therefore, it is necessary to continue to focus our efforts on the in-depth study of PACS manifestations and pathogenesis, in order to uncover typical structural and neuropsychological changes as representation of PACS. (Ceban et al., 2022; Quan et al., 2023; Zhao et al., 2023; Möller et al., 2023).

## 2. Objectives

The aim of the current study is to present a case series of four subjects, two men and two women, all in early and middle adulthood, who have recovered from a mild COVID 19 infection in the previous year. All four of them reported persisting neuro-psychiatric complaints and showed results below the norm on one of the integrity criteria for neuropsychological testing, as well as enlarged perivascular space on magnetic resonance neuroimaging.

## 3. Design

The study is prospective and includes clinical evaluation, MRI brain scan and neuropsychological testing of a group of patients with residual cognitive complaints after COVID 19 infection. The subjects underwent neuropsychological testing once, at baseline and a second time - approximately 6 months later, at follow-up. The design of the study was set to assess cognitive functions in patients with PACS, as well as their dynamics in time. All enrolled patients signed an informed consent and were informed about the objectives of the study.

## 4. Methods

Our investigative methods included:

1) Clinical interview, collecting data about medical and social history, current complaints, prescribed medications, and cerebral risk factors.
2) Neuropsychological evaluation using a computer-based test – the CogState battery (CAB) with the following subtests:
   - Continuous Paired Associate Learning for delayed visual memory through paired associate learning.
   - Groton Maze timed chase test (GMCT) for speed of visual processing.
   - Groton Maze learning test (GML) for executive function.
   - One-card learning (OCL) and One-back memory (OBM) for working memory.
   - Identification test for attention.
3) Magnetic Resonance Imaging (MRI) of the brain

## 5. Results

**Case 1** is a 32-year male, with master's degree and no known previous illnesses or cerebral risk factors. He recovered from a mild COVID 19 infection in January 2022. He had no need of hospitalization or oxygen supplementation. Eleven months after the acute infection he reported persisting complaints of tiredness and forgetfulness. His MRI brain scan showed evidence of an enlarged left hippocampal perivascular space of 0.2 cm. On neuropsychological testing he showed poorer results on OCL at follow-up (Table 1).

**Case 2** is a 38-year-old male, with master's degree and a comorbidity disease - sleep apnea. During the first test he was not yet diagnosed with sleep apnea and therefore had no treatment for it. However, at follow-up he was on BiPAP therapy and was sleeping better at night with. He had suffered from a mild COVID 19 in November 2022, with no hospitalization or need for oxygen support. 5 months after COVID 19 he had complaints of forgetfulness and fatigue. His brain MRI scan showed evidence of an enlarged right hippocampal perivascular space of 0.2 cm and enlarged PVS at the posterior branch of

the left internal capsule. On neuropsychological testing he showed better results at follow-up, but still below the norm for the working memory test (Table 1).

**Case 3:** A 37-year-old female, with master's degree and no known previous illnesses or cerebral risk factors. She recovered from a mild COVID 19 infection in November 2022, with no need of oxygen support or hospitalization. 5 moths later during clinical interview she reported persisting complaints of forgetfulness and absent-mindedness. Her MRI brain scan showed enlarged left hippocampal perivascular space of 0.2 cm. On neuropsychological testing she showed slight decrease on the tests for working memory at follow-up (Table 1).

**Case 4:** A 53-year-old female, with bachelor's degree and no known previous illnesses or cerebral risk factors. She recovered from a mild COVID 19 infection in November 2022. She was not hospitalized and had no need of oxygen supplementation. 5 months later she, as well, was complaining of forgetfulness and absent-mindedness. Similarly, her MRI scan showed enlarged left hippocampal perivascular space of 0.3 cm, as well as a 0.3 cm lacunar hypodense area in the left frontal lobe. Neuropsychological testing showed poorer results OCL at follow-up (Table 1).

**Final results:**

- All four subjects were healthy individuals with no neuro-psychiatric complaints prior to their COVID 19 infection.
- All four subjects suffered from a mild COVID 19 infection, none required oxygen support or hospitalization.
- During the convalescent phase all of them experienced non-specific complaint of fatigue, forgetfulness and impaired concentration.
- Two of the patients performed worse on the test One-card learning at follow-up on both outcome measures - correct and incorrect responses (Figures 1 and 2).
- In all four cases One back accuracy was lower (> 53%) than expected in healthy adults (> 70%) (https://www.cogstate.com).
- All four subjects showed similar changes on MRI brain scan. An enlarged hippocampal perivascular space, ranging from 0.2 to 0.3 cm, was registered on non-contrast MRI.

In General, we encountered the greatest difficulty in the performance of One Back Memory Test where we ask the patient - "Is the previous card the same?". The test assesses orking memory on the base of an n-back paradigm. The Outcome measure we report here is accuracy of performance, that represents the arcsine transformation of the square root of the proportion of correct responses (https://www.cogstate.com).

## 6. Discussion

Our four patients are part of a larger sample of 68 subjects with persisting Long-COVID, that were tested twice, using a very sensitive computer-based neuropsychological battery – once at baseline and once 6 to 9 months later. The results showed similar cognitive impairments, affecting predominantly working memory, which is crucial for the executive functions of the individual. Thus, we confirmed that their subjective complaints had objective findings.

This result is consistent with meta-analytic data of Crivelli et al. (2022), analysing the influence of COVID-19 infection on the cognition up to 7 months after the disease. Their results show statistically significant difference in Montreal Cognitive Assessment (MoCA) score when patients were compared with healthy controls for impairments in memory and executive functions.

Moreover, all four subjects had almost identical changes on their MRI scan, showing hippocampal enlarged perivascular space (H-EPVS). According to Jae Eun Sim et al. (2020), the degree of H-EPVS was not associated with sex, smoking, alcohol consumption, hypercholesterolemia, depression, or coronary heart disease. There was however a positive correlation between H-EPVS and age, so the authors suggested that H-EPVS might be a secondary event, following medial temporal atrophy, which is independently associated with cognitive functions. Given the young age of our subjects and the lack of comorbidities we assume that H-EPVS was not associated with age or cerebrovascular risk factors. Therefore, we can hypothesize that the brain MRI abnormalities might be a structural presentation of PACS.

## 7. Conclusions

Based on the described case series we can conclude that subjective complaints in PACS could be associated with objective findings. Although we can use non-contrast MRI to detect slight structural changes of the brain, the assessment of cognitive functions is proving to be a rather challenging task, that requires sensitive, well-chosen and thorough neuro-psychological tests.

Our study may contribute to further elucidating the mechanisms of long-term cognitive complaints in post-Covid in adults.

*Table 1. Outcome measures for task performance (CogState Brief Battery) in cases reported.*

| Name of task | Correct at baseline | Correct at follow-up | Errors at baseline | Errors at follow-up |
|---|---|---|---|---|
| **Detection** | | | | |
| Case 1 | 35 | 35 | 0 | 0 |
| Case 2 | 35 | 36 | 0 | 1 |
| Case 3 | 35 | 35 | 0 | 0 |
| Case 4 | 35 | 35 | 0 | 2 |
| **Identification** | | | | |
| Case 1 | 30 | 30 | 0 | 1 |
| Case 2 | 30 | 31 | 0 | 1 |
| Case 3 | 30 | 30 | 0 | 1 |
| Case 4 | 30 | 30 | 0 | 1 |
| **One-card learning** | | | | |
| Case 1 | 63 | 56 | 17 | 25 |
| Case 2 | 58 | 68 | 23 | 12 |
| Case 3 | 60 | 64 | 20 | 16 |
| Case 4 | 66 | 58 | 14 | 22 |
| **Working memory** | | | | |
| Case 1 | 31 | 31 | 0 | 0 |
| Case 2 | 31 | 31 | 4 | 0 |
| Case 3 | 31 | 31 | 0 | 1 |
| Case 4 | 31 | 31 | 0 | 2 |

*Figure 1. Outcome measure Case 1.*

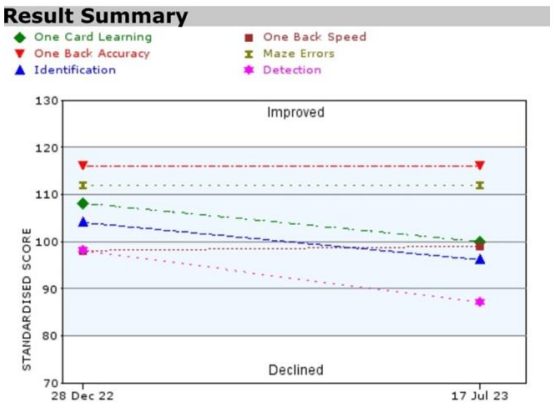
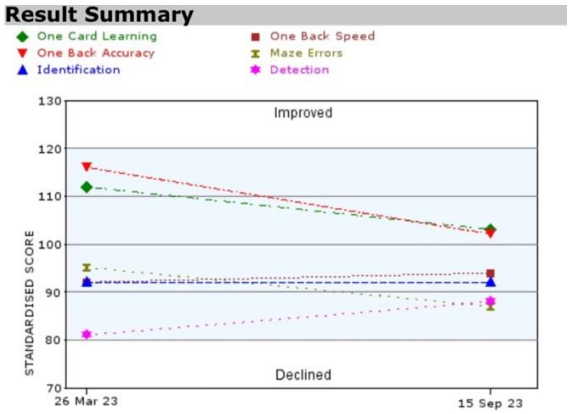



*Figure 2. Outcome measure Case 4.*




*Acknowledgments*

This work was conducted as a part of a larger study, titled “Cognitive impairments as a symptom of PACS in the Bulgarian population”. The study was funded by Medical University of Plovdiv under grant number № ДПДП-12/2022

## *References*

Altuna, M., Sánchez-Saudinós, M. B., & Lleó, A. (2021) Cognitive symptoms after COVID-19, *Neurology Perspectives, 1*(Supplement 1), S16-S24, https://doi.org/10.1016/j.neurop.2021.10.005

Ceban, F., Ling, S., Lui, L. M., Lee, Y., Gill, H., Teopiz, K. M., ... & McIntyre, R. S. (2022). Fatigue and cognitive impairment in post-COVID-19 Syndrome: A systematic review and meta-analysis. *Brain, behavior, and Immunity*, *101*, 93-135.

Crivelli, L., Palmer, K., Calandri, I., Guekht, A., Beghi, E., Carroll, W., ... & Kivipelto, M. (2022). Changes in cognitive functioning after COVID-19: A systematic review and meta-analysis. *Alzheimer's & Dementia*, *18*(5), 1047-1066.

Möller, M., Borg, K., Janson, C., Lerm, M., Normark, J., & Niward, K. (2023). Cognitive dysfunction in post-COVID-19 condition: Mechanisms, management, and rehabilitation. *Journal of Internal Medicine*, *294*(5), 563-581.

Quan, M., Wang, X., Gong, M., Wang, Q., Li, Y., & Jia, J. (2023). Post-COVID cognitive dysfunction: current status and research recommendations for high-risk population. *The Lancet Regional Health–Western Pacific*, *38*. https://doi.org/10.1016/j.lanwpc.2023.100836

Sim, J. E., Park, M. S., Shin, H. Y., Jang, H. S., Won, H. H., Seo, S. W., Seo, W. K., Kim, B. J., & Kim, G. M. (2020). Correlation Between Hippocampal Enlarged Perivascular Spaces and Cognition in Non-dementic Elderly Population. *Frontiers in Neurology, 11*, 542511.

Walle-Hansen, M. M., Ranhoff, A. H., Mellingsæter, M., Wang-Hansen, M. S., & Myrstad, M. (2021). Health-related quality of life, functional decline, and long-term mortality in older patients following hospitalisation due to COVID-19. *BMC Geriatrics*, *21*(1), 199. https://doi.org/10.1186/s12877-021-02140-x

Woo, M. S., Malsy, J., Pöttgen, J., Seddiq Zai, S., Ufer, F., Hadjilaou, A., Schmiedel, S., Addo, M. M., Gerloff, C., Heesen, C., Schulze Zur Wiesch, J., & Friese, M. A. (2020) Frequent neurocognitive deficits after recovery from mild COVID-19. *Brain Communications*, *2*(2), fcaa205.

Zhao, S., Toniolo, S., Hampshire, A., & Husain, M. (2023). Effects of COVID-19 on cognition and brain health. *Trends in Cognitive Sciences*, *27*(11), 1053-1067.