Journal of Clinical Neuroscience 87 (2021) 153–155

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Case report

COVID-19-related cognitive dysfunction may be associated with transient disruption in the DLPFC glutamatergic pathway

Umit Haluk Yesilkaya, Meltem Sen, Yasin Hasan Balcioglu *

Department of Psychiatry, Bakirkoy Prof Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery, Istanbul, Turkey

ARTICLE INFO

Article history:
Received 25 December 2020
Accepted 9 March 2021

Keywords:
Coronavirus
COVID-19
Cognitive dysfunction
Magnetic resonance spectroscopy
Neuropsychiatric symptoms
Viral encephalitis

ABSTRACT

Cognitive impairment has recently attracted researchers as one of the possible neuropsychiatric manifestations of COVID-19, although how the infection perpetuates impairment of cognitive functions is still obscure. We presented a 29-year-old male patient with COVID-19 who developed new-onset transient attention deficit and memory problems following a SARS-CoV-2 infection. Structural neuroimaging was normal. MR-spectroscopy (MRS) of the bilateral DLPFC revealed significant for decreased levels of N-acetylaspartate (NAA), glutamate, and glutamate/glutamine ratio. After a follow-up without any medical treatment but with suggestions of memory exercises for three months a control MRS screening of DLPFC showed improved levels of NAA, glutamate, and glutamate/glutamine ratio. This report may suggest that cognitive deficits in SARS-CoV-2 infection can result from glutamatergic dysfunction with decreased NAA and glutamate levels in bilateral DLPFC.

1. Introduction

It has been suggested that SARS-CoV-2 is a potential neurotrophic virus and several central nervous system (CNS) presentations associated with COVID-19 have been reported [1,2]. Recent studies suggest that unbridled inflammation caused by either the virus itself or immunoreactivity led by the infection might be associated with neuropsychiatric outcomes in COVID-19 [2,3]. Cognitive impairment has piqued interest as one of the possible neuropsychiatric manifestations of COVID-19, although how the infection perpetuates impairment of cognitive functions is still obscure [1]. Here, we presented a patient with COVID-19 who developed transient attention deficit and memory problems, which may be related to glutamatergic dysfunction in the dorsolateral prefrontal cortex (DLPFC), with the aim of contributing to the literature for understanding the etiopathogenesis of COVID-19′s neuropsychiatric manifestations.

2. Case report

A 29-year-old post-graduate male patient was confirmed to be SARS-CoV-2 positive by RT-PCR upon his admission to the emergency department with symptoms of cough, fatigue and myalgia. After the patient was treated according to the national COVID-19 treatment protocol with favipravir and azithromycin, his symptoms improved within a week, and a negative RT-PCR result for SARS-CoV-2 was confirmed. Two weeks after the completion of treatment of COVID-19, the patient was admitted to the psychiatry outpatient unit with complaints of difficulty of remembering past experiences, inattention and carelessness. The patient reported no previous background of neurological nor psychiatric diagnosis including an alcohol or substance abuse. Physical and neurological examinations revealed nothing significant. In psychiatric examination, concentration difficulties were noted, and he seemed to hardly find the appropriate words to speak without any articulation problems. Impaired memory-retrieval was evident when testing free recall. Abnormal findings in perception, thought or mood/affection were not identified. The patient was further evaluated with neuropsychological test which was modified according to findings and the test battery was performed by a trained and experienced neuropsychologist. He was subjected to Frontal Assessment Battery (FAB) to assess frontal lobe dysfunction, Global Deterioration Scale (GDS) to stage cognitive decline, Trail Making Test (TMT) (A and B parts) for attention evaluation and California Verbal Learning Test (CVLT) for the assessment of learning and retrieval patterns. The patient's FAB score was 13 and GDS stage was 3. A number of errors were detected in both A and B parts of TMT and the scores were 2 and 4, respectively. The patient repeated 7 words in his first trial of CVLT. Overall, the results sug-

* Corresponding author at: Department of Psychiatry, Bakirkoy Prof Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery, 34147 Istanbul, Turkey.
E-mail address: yhasanbalcioglu@gmail.com (Y.H. Balcioglu).

https://doi.org/10.1016/j.jocn.2021.03.007
0967-5868/

gested impairment in varying spheres of cognition including memory, executive functioning, motor programming, attention and concentration. To exclude any medical conditions, electroencephalography (EEG), computed tomography (CT) and magnetic resonance imaging (MRI) of the brain performed. Any abnormal bioelectrical activity was not evident on EEG, while neither observable structural nor diffusional deficit was shown in both diffusion-weighted and conventional MRIs and CT scans of the brain. Blood screening including folate, vitamin B12 and vitamin D, electrolytes and thyroid functions was performed and nothing significant for any condition that might mimic a cognitive impairment such as nutritional deficiencies, hypothyroidism nor metabolic disturbance was recorded. Any pathology was not identified on the cerebrospinal fluid evaluation through a lumbar puncture. MR-spectroscopy (MRS) of the bilateral DLPFC was performed to exclude any pathology that might affect brain metabolism potentially underlie impaired cognitive functions. The levels of metabolites were as follows: N-acetylaspartate (NAA) was 166,65 and glutamate was 31,54 and glutamate/glutamine ratio was 0,13 (Fig. 1). The levels were measured relative to the signalling of real-part metabolite activity.

The patient was then followed up without any medical treatment but with suggestions of memory exercises for three months. The follow-up MRS of DLPFC at three months was significant for increased glutamate level (88,57), glutamate/glutamine ratio (0,44) and moderately increased NAA (183,14) while the levels of other metabolites did not show a prominent change from the first MRS (Fig. 1). The FAB score was 16 and GDS stage was 1. No error was detected in part A while the patient made 2 errors in part B of TMT. He repeated 11 words in CVLT. No neurologic nor cognitive deficits were detected at the patient's follow-ups.

3. Discussion

The abovementioned patient developed attention and memory deficits concomitant with COVID-19 infection. Cognitive functions are known to be related to glutamatergic activity in the prefrontal cortex, particularly the DLPFC, and hippocampus [4]. Therefore, damage to these brain regions or neurotransmitter dysfunctions are likely to result in cognitive dysfunction. After the SARS-CoV epidemic in 2003, post-mortem studies indicated the presence of the SARS-CoV genome in the cortex and hypothalamus of infected subjects. Additionally, diffuse lesions were identified in several brain regions, including white matter and the subcortical areas of the frontal, temporal and parietal lobes in patients who died from Middle East Respiratory Syndrome (MERS) infection [5]. In animal studies, it has been shown that coronaviruses cause neurodegeneration in the hippocampal CA1 and CA3 areas, leading to a decrease in short-term learning and impairment in spatial memory [6]. Corroborating these data, Lu et al. showed hippocampal changes in brain images of SARS-CoV-2 infected patients, which correlated with a loss of memory [7]. Considering previous findings, impairment of cognitive functions that regulated by the DLPFC may be attributed to SARS-CoV-2 infection in our patient.

Glutamate is the main neurotransmitter involved in cognitive functions in the frontal cortex and hippocampus. In previous research, the levels of glutamate were found to be decreased with other viral infections of the CNS, such as HIV-related dementia [8]

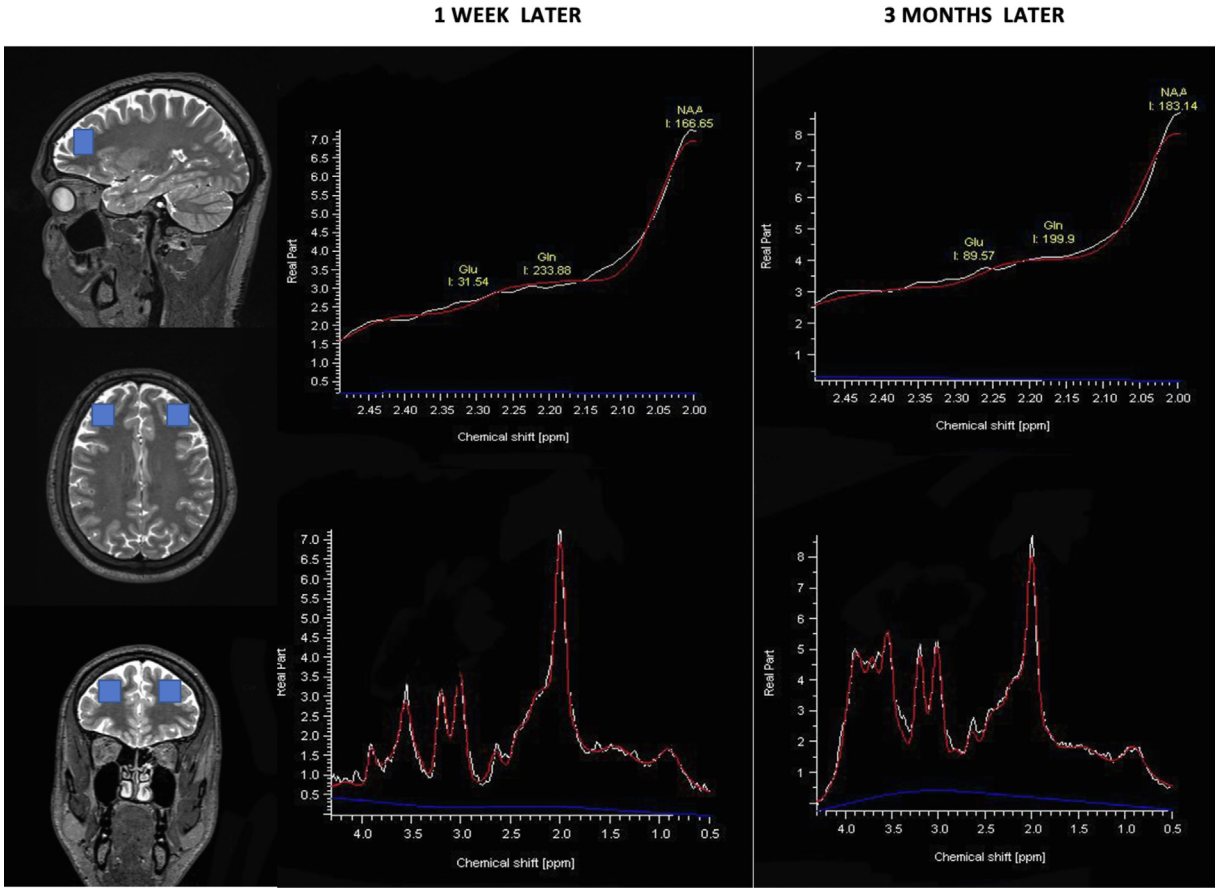

Fig. 1. Alterations in glutamate (*Glu*), glutamine (*Gln*) and N-acetylaspartate (*NAA*) levels at a week and three months later the initial diagnosis of SARS-CoV-2 infection.

which has been associated with metabolic derangement [9]. Congruently, Crunfli et al. have suggested that the redeployment of metabolism in SARS-CoV-2-infected astrocytes may be associated with a disruption within the glutamatergic pathway. [10]. In the index patient, the altered glutamate/glutamine ratio may further support a dysregulated glutamatergic pathway possibly associated with the CNS involvement of SARS-CoV-2. In addition, NAA is known to be involved in cognitive functions [11], and the patient initially showed low levels of NAA, which was spontaneously rebalanced at the follow-up that overlaps the recovery phase of the SARS-CoV-2 infection. This finding also lends credence our hypothesis that cognitive dysfunction might be associated with COVID-19.

Overall, our findings suggest that cognitive deficits in SARS-CoV-2 infection can result from glutamatergic dysfunction with decreased glutamate and NAA levels in the DLPFC confirmed by MRS. Of note, this dysfunction seemed to be reversible. In fact, current evidence is not encouraging that favipravir and azithromycin are likely to lead such a cognitive impairment. Moreover, cognitive impairment in COVID-19 resulting from disrupted glutamatergic pathway may be alleviated with the use of therapeutics that increase glutamate levels such as N-acetylcysteine [11,12] and glutathione [13]. However, further research is warranted to validate the authenticity of this suggestive etiopathogenesis of neuropsychiatric outcomes of COVID-19 along with the proposed treatment strategy.

4. Ethical declaration

Informed consent was obtained from the patient following an explanation provided on the need to request permission for use of his clinical information in a scientific work.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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