

LETTER TO THE EDITOR

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Persistent cognitive impairment associated with cerebrospinal fluid anti-SARS-CoV-2 antibodies six months after mild COVID-19

Max Borsche^{1,2}, Dirk Reichel³, Anja Fellbrich², Anne S. Lixenfeld⁴, Johann Rahmüller^{4,5}, Eva-Juliane Vollstedt¹, Bandik Föh^{4,6}, Alexander Balck^{1,2}, Christine Klein¹, Marc Ehlers⁴ and Andreas Moser^{2,7*} 

Abstract

Neurological long-term sequelae are increasingly considered an important challenge in the recent COVID-19 pandemic. However, most evidence for neurological symptoms after SARS-CoV-2 infection and central nervous system invasion of the virus stems from individuals severely affected in the acute phase of the disease. Here, we report long-lasting cognitive impairment along with persistent cerebrospinal fluid anti-SARS-CoV-2 antibodies in a female patient with unremarkable standard examination 6 months after mild COVID-19, supporting the implementation of neuropsychological testing and specific cerebrospinal fluid investigation also in patients with a relatively mild acute disease phase.

Keywords: COVID-19, SARS-CoV-2, Neurologic sequelae, Cognitive impairment, CSF antibodies

Introduction

There is mounting evidence for neurological long-term sequelae after COVID-19 [4]. In the majority of COVID-19 cases exhibiting neurological impairment reported thus far, symptoms were monitored in the acute disease phase and predominantly in hospitalized and severely affected patients [3]. However, neurological long-term impairment after critical illness is a well-established phenomenon in the context of acute respiratory distress syndrome [8], especially when intensive care and ventilation are required. Therefore, it currently remains elusive whether neurological symptoms are rather indirectly related to the infection as a general consequence of critical illness, or whether they are causally related to SARS-CoV-2 infection. Notably, there is evidence for a direct invasion of the central nervous system by the virus [5]

and SARS-CoV-2-specific antibodies were detected in the cerebrospinal fluid (CSF) of patients in the acute phase of severe COVID-19 [1]. Potential neurological long-term impairment after mild disease expression has not been systematically studied to date. This latter approach holds the potential to disentangle possible direct virus-mediated sequelae from non-specific persistent disability following critical illness.

Case description

We report a 57-year-old female with mild but disabling neuropsychological symptoms 6 months after mild COVID-19. During the acute infection, the patient self-referred to a hospital after a positive result of SARS-CoV-2 PCR-testing, which was performed in an outpatient setting due to fever, headache, ubiquitous limb pain, and diarrhea. Upon admittance, vital parameters including peripheral oxygen levels were normal. Laboratory routine examinations were unremarkable despite slightly increased levels of C-reactive protein. Neither intensive care, nor ventilation were required during the hospitalization, and she was discharged home after 5 days. Two weeks after the acute

* Correspondence: andreas.moser@neuro.uni-luebeck.de

²Department of Neurology, University of Lübeck and University Medical Center of Schleswig-Holstein, Campus Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany

⁷Center of Brain, Behavior and Metabolism, University of Lübeck, Lübeck, Germany

Full list of author information is available at the end of the article



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illness, she experienced impaired concentration and action planning. As this condition persisted for several months, preventing her from resuming her professional activity as a nurse and limiting herself in the organization of her activities of daily living, she was referred to our university hospital by a local neurologist. A detailed neurological examination did not detect any abnormalities. In particular, no apraxia or aphasia, and no hypokinetic-rigid signs were found. Apart from a depressive episode in the past, her medical history was unremarkable. A brain MRI examination, standardized testing of the olfactory function (Supplement – BSIT), serologic examination for infectious and autoimmune disease, and further laboratory examinations were likewise normal (Supplement - Laboratory analysis). Workup for both synaptic and paraneoplastic antineuronal antibodies, investigated in serum, was negative (Supplement – Antineuronal antibodies). CSF routine examination was unremarkable, except for a non-specific elevation of CSF protein levels (Supplement – Standard CSF analysis). However, an in-depth standardized neuropsychological assessment revealed relevant impairment regarding “attention”, “alertness” and “working memory”, and the patient scored high on distress and fatigue assessments (Supplementary Table 1). Serologic investigations (Supplement – Methods) revealed positive IgG antibody titers against the S1 (4.2) and the nucleocapsid (NCP) protein (1.7) of SARS-CoV-2 (EUROIMMUN, Lübeck, Germany, values < 0.8 are considered negative, 0.8–1.1 borderline, > 1.1 positive). In comparison to healthy control subjects ($n = 2$), we detected elevated levels of SARS-CoV-2-specific IgG S1 antibodies and a trend towards elevated IgG nucleocapsid antibodies in the CSF (Table 1; Supplement – Methods). Furthermore, as neurotransmitter alterations have been reported in individuals with mild cognitive impairment [6] and animal models of coronavirus infection [2], we investigated levels

Table 1 CSF SARS-CoV-2-specific IgG antibodies against the spike (S1) and the nucleocapsid (NCP) protein and neurotransmitter levels in the index patient compared to control subjects

	Index patient	Control subjects	P value
CSF SARS-CoV-2 antibodies			
IgG anti-S1, 1:2	0.450	0.044 +/- 0.009 ($n = 2$)	0.017
IgG anti-S1, 1:5	0.190	0.039 +/- 0.009 ($n = 2$)	0.048
IgG anti-NCP, 1:2	0.150	0.036 +/- 0.015 ($n = 2$)	0.102
IgG anti-NCP, 1:5	0.073	0.024 +/- 0.007 ($n = 2$)	0.114
CSF neurotransmitter levels			
Glutamate (μM)	3.70	4.53 +/- 0.82 ($n = 3$)	0.546
GABA (μM)	0.30	0.32 +/- 0.02 ($n = 3$)	0.434
Glutamine (μM)	604	634 +/- 82 ($n = 3$)	0.820

Mean +/- standard deviation is shown. Differences were assessed using student's t-test. $p < 0.05$ was considered significant
GABA Gamma-aminobutyric acid

of gamma-aminobutyric acid (GABA), glutamate, and glutamine in the CSF (Supplement – Methods), but did not observe any significant differences between the index patient and controls subjects ($n = 3$) (Table 1).

Discussion

In conclusion, we demonstrate long-lasting neuropsychologic sequelae along with persistent SARS-CoV-2-specific CSF antibodies several months after a relatively mild acute disease course and encourage the investigation of CSF SARS-CoV-2-specific antibodies and neuropsychological testing to detect possible ‘Long COVID’. Given the mounting evidence for neurological sequelae including cognitive impairment after acute SARS-CoV-2 infection [7], the increasing number of individuals seeking help from neurologists must be expected to become a significant challenge during and after the pandemic. Of note, such complaints were more frequent in, but not limited to severe cases [9], pointing to a relevant role of mild acute SARS-CoV-2 infections in neurological ‘Long COVID’. Our case highlights that investigations beyond routine clinical and laboratory assessment are necessary to identify subtle but clinically relevant sequelae of COVID-19 and that the study of large cohorts for the presence of long-term mild impairment and associated immunological changes is warranted in a longitudinal case-control design.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s42466-021-00135-y>.

Additional file 1.

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Authors' contributions

MB, ME, and AM conceptualized the study. MB, DR, EJV, ASL, JR, AB, BF, ME and AM contributed to the organization of the study, data collection and data analysis. MB drafted the first version of the manuscript. AB, BF, CK, ME, and AM critically revised the manuscript. All authors read and approved the final version of the manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Consent for publication

Written informed consent for this study was obtained from the index patient and the control subjects and the ethics committee of the University of Lübeck approved the study.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Institute of Neurogenetics, University of Lübeck, Lübeck, Germany. ²Department of Neurology, University of Lübeck and University Medical Center of Schleswig-Holstein, Campus Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany. ³Outpatient Practice for Neurology and Psychiatry, Lübeck, Germany. ⁴Institute of Nutritional Medicine, University of Lübeck and University Medical Center of Schleswig-Holstein, Lübeck, Germany. ⁵Department of Anesthesiology and Intensive Care, University of Lübeck and University Medical Center of Schleswig-Holstein, Lübeck, Germany. ⁶Department of Medicine I, University Medical Center Schleswig-Holstein, Campus Lübeck, Lübeck, Germany. ⁷Center of Brain, Behavior and Metabolism, University of Lübeck, Lübeck, Germany.

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