



A case of anterograde amnesia in an MS-like demyelination after COVID-19

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To the Editor,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulting in COVID-19, can affect respiratory, circulatory, and digestive systems. Central nervous system (CNS) involvement has also been documented: cases of COVID-19-related CNS inflammatory syndromes, stroke, encephalopathies (delirium/psychosis), and Guillain-Barré syndrome have been indeed reported [1]. Furthermore, increasing evidence that patients with SARS-CoV-2 can present with memory, attention, information processing, and executive disorders is now available [2].

Case report

We report the case of MK, a 51-year-old, right-handed woman, with 8 years of education suffering from Hashimoto's thyroiditis and with a homozygosity for the G20210A mutation in the prothrombin gene. On March 15, she was admitted to the emergency room of the local Hospital for fever and respiratory signs. Nasopharyngeal sample for SARS-CoV-2 resulted positive and, on March 16, the patient was transferred to the COVID-Unit of a different Hospital where a chest X-ray scan showed interstitial pneumonia.

Thereafter, due to the continuous worsening of her respiratory signs, on the same day, MK was transferred to the High Intensity Medicine Department. During the hospitalization, she was treated with O₂, antivirals, tocilizumab, dexamethasone, hydroxychloroquine, and ceftriaxone. New nasopharyngeal samples for SARS-CoV-2 collected on March 29 and 31 resulted negative and, on March 30, the patient was transferred to a long-term care unit in Trento. She was finally discharged on April 24 and she resumed her job in a canteen on August 5.

On January 7, 2021, she was enrolled in a study protocol investigating the neurological and neuropsychological consequences of COVID-19. The neurological examination performed on the same day resulted negative except for a cramp-like symptomatology in the lower limbs: subsequent EMG/ENG examinations were found to be normal. On January 20, as a part of the abovementioned study protocol, MK was referred to our Center for Neurocognitive Rehabilitation (CeRiN) in Rovereto for a comprehensive neuropsychological assessment. During the clinical interview, she complained of hyposmia and dysgeusia arisen immediately after SARS-CoV-2 infection and still persistent. She also reported episodes of smell misperception (i.e., smell of burning even though nothing around was on fire) causing discomfort, especially at work. Furthermore, a clinical standardized scale revealed the presence of *fatigue* which, together with the referred persistence of asthenia and dyspnoea from exercise (i.e., going upstairs), was further reason of discomfort at work. MK complained also of episodic and prospective memory disorders, difficulty in concentrating, and, due to these problems, uncertainty in performing daily activities (even if ADLs and IADLs were fully preserved). Reduced occupational and functional outcomes, as well as subjective cognitive complaints and concerns about her own health, produced mild depression, in the absence of anxious or PTSD symptomatology. The neuropsychological examination confirmed the memory disturbances: immediate recall of a list of non-semantically related words was normal,

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while delayed recall was found to be severely impaired; in the recognition trial, MK recognized correctly the 73.3% of the stimuli, without any false positive. Visual long-term memory was borderline, while, in the recognition trial, she performed below the cutoff (true positive: 50%). Verbal short-term span was found to be normal while spatial span resulted borderline. MK's performance was instead largely preserved in tests evaluating attention, executive functions, visuo-spatial, visuo-perceptive, and visuo-constructional abilities. Her oral production was fluent both with reference to spontaneous and elicited tasks; oral comprehension was intact too. MK's premorbid level of intelligence and non-verbal reasoning abilities were within the normal values too (see Table 1 in the Appendix).

An MRI performed on January 20 revealed, on the long TR sequences, some areas of hyperintensity of signal in the paracallosal and periventricular white matter, recognizable as hypointense areas in T1-dependent images, devoid of hypointense deposits in SWI sequences, but with perivenular distribution, and therefore suggestive of an inflammatory

pathology. An EEG, performed in the following days, was instead normal. Due to this MRI result, on February 7, MK was admitted to the Neurology Department of the Rovereto Hospital for further investigations. In particular, a further MRI with paramagnetic contrast medium performed on February 8 confirmed an unchanged morphology and size of the lesions observed at the previous MRI, without contrast enhancement of the gliotic areas. No areas of impaired signal in the spinal cord, from the cervical-dorsal tract up to the medullary cauda, emerged from T2-weighted images. Cerebrospinal fluid and serum examination resulted positive for oligoclonal bands ("mirror pattern", type 3). MK was then dismissed with the diagnosis of "long-COVID with neurological manifestations (hyposmia and dysgeusia), and suspected CNS inflammatory syndrome under definition." During the post-hospitalization, she was also submitted to a total-body PET-CT which showed cortical hypometabolism, except for the occipital lobes (see Fig. 1).

Finally, on May 7, MK returned to our Neurocognitive Rehabilitation Center for further testing. The neurological

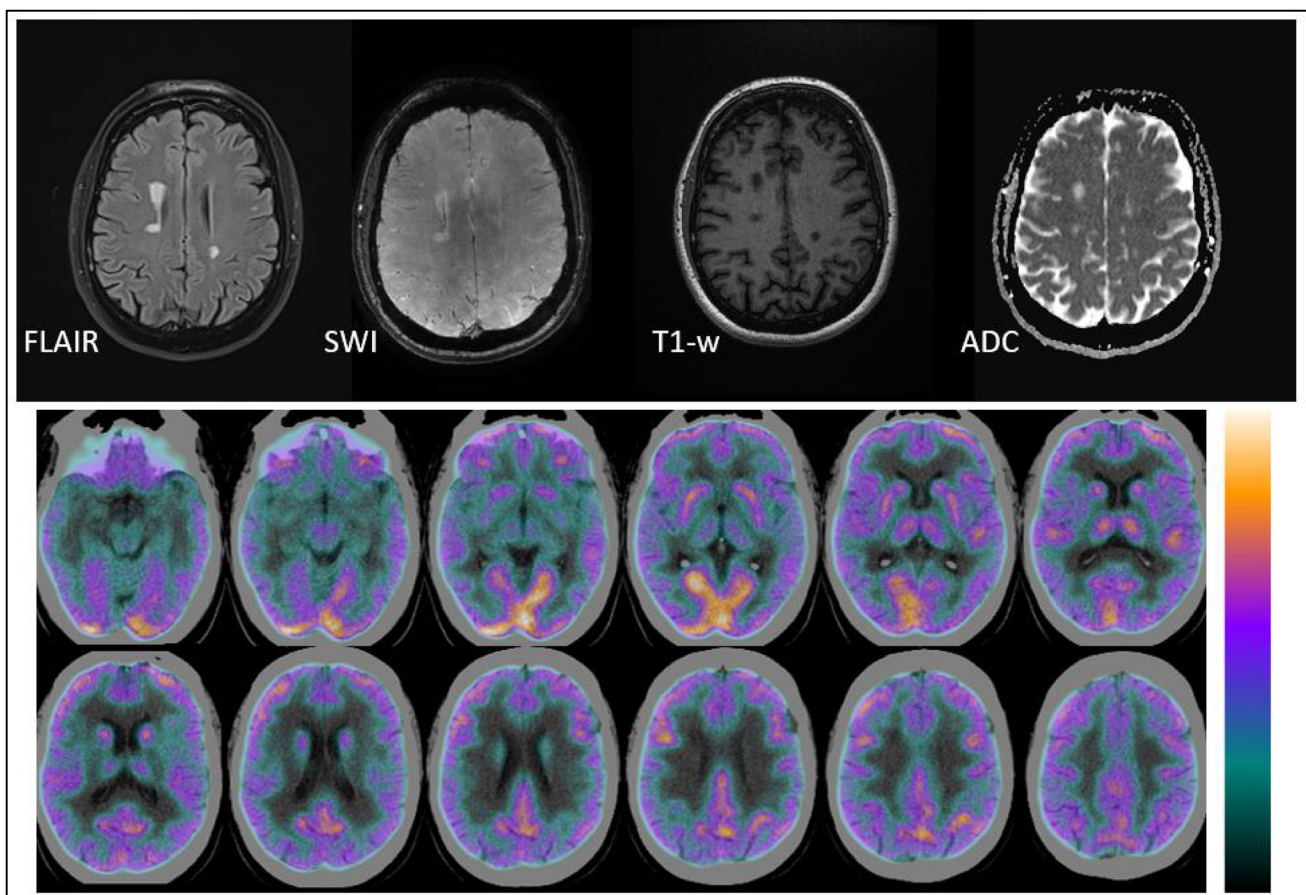


Fig. 1 Top row: axial FLAIR, SWI, T1-weighted, and ADC MRI sequences. Long TR sequences revealed areas of hyperintensity of signal in the paracallosal and periventricular white matter, recognizable as hypointense areas in T1-dependent images and devoid of

hypointense deposits in SWI sequences, but with perivenular distribution. Bottom row: 18F-FDG PET-CT brain scans showing cortical hypometabolism, except for the occipital lobes

examination revealed a torpid corneal reflex and a pronator drift both on the right side. Furthermore, reflexes were found to be hypo-excitabile in the upper limbs, while patellar reflexes resulted left > right and Achilles reflex absent bilaterally. During the clinical interview, she complained of the persistence of discomfort in her job caused by both *fatigue* and hyposmia (in particular), and dysgeusia. She also referred the persistence of memory disturbance and difficulty concentrating. Furthermore, even if a clinical scale did not reveal any depressive (or anxious) symptoms, the clinical interview highlighted very strong concern about her own health. At the neuropsychological examination, MK's performance resulted largely preserved on screening, attention, information processing, and executive tests; recognition memory was preserved as well. The general memory index obtained in an ecologically valid memory battery resulted instead below the cutoff: pathological scores were found in the verbal (i.e., immediate and delayed story recall) and prospective memory subtest of the battery (see Table 2 in the Appendix). To sum up, the neuropsychological evaluation confirmed the memory disorders complained by MK which have been frequently reported in cases of CNS demyelination. These deficits, together with *fatigue* and smell misperceptions, were cause of insecurity in performing daily activities.

Discussion

It is worth mentioning that MK's neurological complaints and neuropsychological disorders appeared after virus neutralization (no cognitive deficit was indeed reported before

SARS-CoV-2 infection) and persisted until today. With this regard, evidence that focal neuropsychological disorders can be present even when SARS-CoV-2 is not active anymore is now available (for instance, [3]). Furthermore, literature on cognitive disorders in acute respiratory distress syndrome (ARDS) reports that up to 78% ARDS patients had cognitive problems 1 year post-discharge and approximately 50% at 2 years; self-reported everyday memory failures have been instead documented to persist 5 years post-discharge. Lasting cognitive impairments have also been reported in a proportion of those who have spent time in intensive care. Taken together, these data may suggest that enduring cognitive deficits are likely to be common in people who suffered severe forms of COVID-19 (even without an obvious neurological presentation in the acute stage), and who have been admitted to intensive care [2].

Finally, the case of MK also shows that it is likely that the SARS-CoV-2 infection has produced an inflammatory response with a CNS demyelination. Stress is a trigger for autoimmunity, including MS, and major stressful life events have been associated with an increased risk of developing MS [4]. In the very recent literature, three cases of MS-like demyelination with an atypical presentation associated with COVID-19 have been reported ([5] for review): indeed, in one case MRI lesions were round in shape and larger than typical MS plaques; in another case, lesions were located mainly in the deep white matter and subcortical areas; finally, in the remaining case, despite the presentation with optic neuritis, the associated field defect rendered the presentation atypical. To our knowledge, MK represents the first case of an MS-like demyelination with typical plaques developed after COVID-19 neutralization where an anterograde amnesia is described.

Appendix

Table 1 Synthesis of the performance obtained by MK at the first neuropsychological examination. Pathological performances are underlined

	Range	Corrected score	Cutoff	Diagnosis
Memory				
Digit span – forward	0–9	4.75	< 4.26	Normal
Digit span – Backward	0–8	2.71	< 2.65	Borderline
Corsi block-tapping task	0–9	3.74	< 3.46	Borderline
Rey auditory-verbal learning task				
-Immediate recall	0–75	35.5	< 28.53	Normal
- <u>Delayed recall</u>	<u>0–15</u>	4	<u>< 4.69</u>	<u>Pathological</u>
-Recognition trial: true positives	0–15	11	-	-
-Recognition trial: false positives	0–15	0	-	-
Modified Taylor Complex Figure (MTFC)				
-Delayed recall	0–36	10.4	< 8.41	Borderline
- <u>Recognition trial: true positives</u>	<u>0–10</u>	<u>5.97</u>	<u>< 7.16</u>	<u>Pathological</u>

Table 1 (continued)

	Range	Corrected score	Cutoff	Diagnosis
Attention				
Multiple features target cancelation (MFTC)				
-Points	0–13	12	-	-
-False alarms	0–67	1.32	> 2.77	Normal
-Time	0–∞	51.04	> 135.7	Normal
-Accuracy	0–100%	98%	< 86.9%	Normal
Trail making test (TMT)				
-Part A	0–∞	40	> 94	Normal
-Part B	0–∞	126	> 282	Normal
-Part B-A	0–∞	83	> 187	Normal
Symbol digit test (SDT)	0–115	37	< 31	Normal
Executive functions				
Frontal assessment battery (FAB)	0–18	15.2	≤ 13.4	Normal
Stroop test				
-Errors	0–90	2.25	≥ 4.24	Normal
-Time	0–∞	19.5	≥ 36.92	Normal
Phonemic verbal fluency task	0–∞	26	< 17	Normal
Language				
Oral naming	0–48	46.67	< 41.49	Normal
Semantic verbal fluency task	0–∞	35	< 27.67	Normal
Token test	0–36	33	< 29	Normal
Visuo-spatial, visuo-perceptive and visuo-constructional abilities				
Benton's judgment of line orientation test	0–30	29	< 19	Normal
Benton's facial recognition test	0–54	43	< 39	Normal
Modified Taylor Complex Figure (MTCF)				
-Immediate recall	0–36	33.7	< 27.67	Normal
Reasoning and IQ				
Raven's Coloured Progressive Matrices (CPM-47)	0–36	31.8	< 18.96	Normal
Short intelligence test (TIB)				
-Total IQ estimation	-	108.495	< 93.1	Normal
Neuropsychiatric and functional assessment				
Hospital Anxiety and Depression Scale (HADS)				
-Anxiety	0–21	4	> 7	Normal
-Depression	0–21	8	≥ 7	Pathological
COVID-19-PTSD Questionnaire	0–76	12	≥ 26	Normal
Fatigue Severity Scale – FSS	0–7	5.77	≥ 4.67	Pathological
ADLs	0–6	6	≤ 5	Normal
IADLs	0–8	8	≤ 7	Normal

Table 2 Synthesis of the performance obtained by MK at the second neuropsychological examination. Pathological performances are underlined

	Range	Corrected/z score	Cutoff	Diagnosis
Screening				
Rao’s Brief Repeatable Battery of Neuropsychological Tests (BRB-NT) (version A)				
-Selective Reminding Test, Long-Term Storage (SRT-LTS)	0–72	$z = -0.57$	2 sd	Normal
- Selective Reminding Test, Consistent Long-Term Consolidation (SRT-CLTR)	0–72	$z = -0.99$	2 sd	Normal
-10/36 Spatial Recall Test (SPART)	0–30	$z = -1.81$	2 sd	Borderline
-Symbol Digit Modalities Test (SDMT)	0–110	$z = -0.30$	2 sd	Normal
-Paced Auditory Serial Addition Test (PASAT-3)	0–60	$z = -0.94$	2 sd	Normal
-Paced Auditory Serial Addition Test (PASAT-2)	0–60	$z = -1$	2 sd	Normal
-Delayed Recall of the Selective Reminding Test (SRT-D)	0–12	$z = -1.31$	2 sd	Normal
-Delayed Recall of the 10/36 Spatial Recall Test (SPART-D)	0–10	$z = -0.91$	2 sd	Normal
-Word List Generation (WLG)	0–∞	$z = 0.5$	2 sd	Normal
Attention				
Open-source Open-access Reaction Time Test (OORTT)				
-Single Reaction Time (SRT)	0–2500	262.50	≥403	Normal
-Go/No-go (GNG)	0–2500	391.30	≥542	Normal
-Four-Position Reaction Time, Left Superior quadrant (4PRT-LS)	0–2500	236	≥446	Normal
-Four-Position Reaction Time, Right Superior quadrant (4PRT-RS)	0–2500	259	≥412	Normal
-Four-Position Reaction Time, Left Inferior quadrant (4PRT-LI)	0–2500	226.20	≥436	Normal
-Four-Position Reaction Time, Right Inferior quadrant (4PRT-RI)	0–2500	253.20	≥385	Normal
Executive functions				
Tower of London (ToL)				
-Time	0–36	$z = 0.51$	2 sd	Normal
-Accuracy	0–36	$z = 0.86$	2 sd	Normal
Wisconsin Card Sorting Test (WCST)				
-Completed categories	0–6	$z = 0.4$	2 sd	Normal
-Perseverative errors	0–128	$z = -0.06$	2 sd	Normal
-Non-perseverative errors	0–128	$z = -1.44$	2 sd	Normal
-Learning from the task	-	$z = -1.01$	2 sd	Normal
Memory				
Recognition memory test				
-Words	0–30	25.14	≤22.47	Normal
-Buildings	0–30	28.14	≤21.41	Normal
<u>Rivermead Behavioural Memory Test (RMBT-3): General Memory Index (GMI)</u>				
	<u>51–147</u>	<u>66</u>	<u>≤70</u>	<u>Pathological</u>
	Range	PP score	Cutoff	Diagnosis
<u>-Names</u>	<u>0–8</u>	<u>3</u>	<u>PP < 4</u>	<u>Pathological</u>
-Belongings	0–8	4	PP < 4	Borderline
-Appointments	0–4	13	PP < 4	Normal
-Picture Recognition – delayed	0–15	12	PP < 4	Normal
-Story recall – immediate	0–21	4	PP < 4	Borderline
<u>-Story recall – delayed</u>	<u>0–21</u>	<u>3</u>	<u>PP < 4</u>	<u>Pathological</u>
-Face recognition – delayed	0–15	9	PP < 4	Normal
-Route recall – immediate	0–13	8	PP < 4	Normal
-Route recall – delayed	0–13	8	PP < 4	Normal
<u>-Messages – immediate</u>	<u>0–6</u>	<u>1</u>	<u>PP < 4</u>	<u>Pathological</u>
<u>-Messages – delayed</u>	<u>0–6</u>	<u>2</u>	<u>PP < 4</u>	<u>Pathological</u>
<u>-Orientation and date</u>	<u>0–14</u>	<u>1</u>	<u>PP < 4</u>	<u>Pathological</u>
-Novel task – immediate	0–51	10	PP < 4	Normal
-Novel task – delayed	0–17	12	PP < 4	Normal
Neuropsychiatric assessment				
	Range	Raw score	Cutoff	Diagnosis

Table 2 (continued)

	Range	Corrected/z score	Cutoff	Diagnosis
Hospital Anxiety and Depression Scale (HADS)				
-Anxiety	0–21	4	>7	Normal
-Depression	0–21	4	>7	Normal
ADLs	0–6	6	≤5	Normal
IADLs	0–8	8	≤7	Normal

Declarations

Ethical approval This study is part of a larger study approved by the Local Ethical Committee.

Informed consent The patient gave her informed consent to participate to the study. The study was conducted according to the principles of the Declaration of Helsinki.

Conflict of interest None.

References

1. Paterson RW, Brown RL, Benjamin L et al (2020) The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain* 143:3104–3120. <https://doi.org/10.1093/brain/awaa240>
2. Wilson BA, Betteridge S, Fish J (2020) Neuropsychological consequences of COVID-19. *Neuropsychol Rehabil* 30:1625–1628. <https://doi.org/10.1080/09602011.2020.1808483>
3. Priftis K, Prior M, Meneghetti L et al (2021) Alexia without agraphia in a post COVID-19 patient with left-hemisphere ischemic stroke. *Neurol Sci* 42:2179–2181. <https://doi.org/10.1007/s10072-021-05211-4>
4. Giordano A, Cetta I, Orrico M et al (2021) Stress related to COVID-19 pandemic as a trigger for disease activity in multiple sclerosis: a case report. *Neurol Sci* 42:3969–3971. <https://doi.org/10.1007/s10072-021-05442-5>
5. Ismail II, Salama S (2021) Association of CNS demyelination and COVID-19 infection: an updated systematic review. *J Neurol*. <https://doi.org/10.1007/s00415-021-10752-x>

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