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Post-Infectious Neurologic Complications in Covid-2019: A Complex Case Report

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PART 1

ABSTRACT

A 40-year-old woman with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection developed neurologic manifestations (confusion, agitation, seizures, dyskinesias, and parkinsonism) few weeks after SARS onset. Magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analyses were unremarkable, but an 18F-Fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) showed limbic and extra-limbic hypermetabolism. A full recovery, alongside FDG normalization in previously hypermetabolic areas, was observed after intravenous immunoglobulin (IVIg) administration.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has to date caused almost 2.500.000 deaths worldwide. Although typically inducing respiratory symptoms, it is a systemic illness with possible neurologic complications. Based on similarities with other Coronaviruses, different central nervous system (CNS) damage mechanisms, ranging from direct CNS infection to dysimmune response (*1*,*2*), have been hypothesized for SARS-CoV-2. However, the pathophysiology of neurological manifestations and the diagnostic role of ancillary investigations remain to be elucidated.

CASE REPORT

The present case study was authorized by the Ethics Committee of the ASST Lariana, Ospedale Sant'Anna of Como, Italy. An informed written consent was provided for the report publication.

An overweight (body-mass index 28.3 kg/m^2) 40-year-old woman, otherwise without any risk factors or comorbidities, was transported to Emergency Department in late March (day 0), because of syncope occurred after few days of fever, anosmia, fatigue, and dyspnea. Arterial blood gas analysis showed severe hypoxemia (PaO2/FiO2 < 200 mmHg). Chest computed tomography (CT) demonstrated diffuse interstitial pulmonary pathology with ground-glass opacities. Nasopharyngeal swab was positive for SARS-CoV-2 RNA. After Intensive Care Unit admission, the patient was sedated, intubated and mechanically ventilated.

On early April (day 14), following sedation discontinuation and extubation, the patient appeared fully alert, although episodically agitated and uncooperative. The day after, the patient worsened significantly, becoming persistently confused and agitated, and showing recurrent generalized tonic-clonic seizures. A brain CT scan was unremarkable, while an electroencephalogram (EEG) showed bilateral slow waves with epileptiform discharges. Blood chemistry tests revealed high C-reactive protein (62.4 mg/L) and increased white blood cell counts (16.92x10^3/uL). Customary cerebrospinal fluid (CSF) analyses were conversely unremarkable, showing normal cellularity (n=2/uL) and protein content (32 mg/dL). A wide screening for antibodies usually associated with autoimmune encephalitis yielded negative results. CSF antibody testing and reverse transcriptase-polymerase chain reaction (RT-PCR) for most common neurotropic viruses was negative. A SARS-CoV-2 RT-PCR performed on CSF was also negative, but CSF was positive for anti-SARS-CoV-2 IgG antibodies and had elevated pro-inflammatory cytokines.

Brain magnetic resonance imaging (MRI) (days 16 and 30) was normal (figures 1 and 2), but a cerebral 18F-Fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) (day 38), using a 3-MBq/Kg 18F-FDG injected activity, revealed increased

metabolism in mesial temporal lobes and subthalamic nuclei (figure 3A), confirmed by statistical parametric mapping (SPM) quantification (figure 3C).

A 5-day intravenous immunoglobulin (IVIg) cycle (0.4 g/kg daily) was started the day after. During the first week of treatment, the patient remained confused and uncooperative. She also developed stereotypical paroxysmal lower limb and choreiform upper limb movements, for which haloperidol was introduced.

From the second week onwards, the patient rapidly improved. In mid-May (day 57), she was described as fully alert, cooperative, and able to communicate fluently. The abnormal movements earlier described had disappeared. Her neurological exam exclusively revealed bradykinesia and postural/action tremor of left upper limb, possibly influenced by ongoing haloperidol treatment. EEG recording was at this time normal. A post-IVIg CSF showed a reduction of previously increased cytokine levels (interleukyne-6, from 47.41 to 0.61 pg/mL; interleukyne-8, from 443.33 to 16.71 pg/mL; interleukyne-9, from 8.66 to 3.38 pg/mL; interleukyne-15, from 103.13 to 73.22 pg/mL) but, unlike the pre-IVIG CSF (figure 4A), was immunoreactive to basal ganglia antigens (figure 4B). A second IVIg cycle was initiated in late June, when the patient was still displaying parkinsonian signs. Haloperidol was discontinued in late July, after gradual tapering. Two weeks later (day 143), no neurological signs nor significant PET abnormalities were any longer noted (figures 3B and 3D).

DISCUSSION

Although neurotropism has previously been reported for other coronaviruses, evidence for direct CNS infection is lacking for SARS-CoV-2. The present case underlines the possibility of a post-

infectious inflammatory brain involvement related to SARS-CoV-2, once alternative infectious or autoimmune brain disorders have been excluded.

As also seen recently in (*3*), while MRI might be insufficient to reveal the cerebral involvement, PET imaging can decisively assist the clinician in making a proper diagnosis and promptly considering an appropriate treatment. The observation of FDG hypermetabolism in subthalamic nuclei may also explain the patient's dyskinesias that, to our knowledge, have not yet been reported among possible SARS-CoV-2 complications. Despite similar conclusions as another case study (*3*) about the diagnostic role of PET imaging, our report differs from (*3*) in several respects. Firstly, we performed imaging and biologic investigations, including an analysis of the cytokine profile, at multiple rather than a single time point. Secondly, our immunological analyses were based on western blotting rather than immunostaining. Finally, we used IVIg, instead of steroids, as immunomodulatory treatment. In both studies, however, there was a tight association of clinical with biologic findings (cerebellar syndrome with immunoreactivity against Purkinje cells in (*3*); parkinsonism with immunoreactivity against striatal neurons in our study) and a favorable response to immunomodulatory therapy.

Unfortunately, a long-lasting stay of SARS-CoV-2 patients in intensive care units may by itself delay an appropriate treatment, since sedation and intubation required to contrast the effects of the primary process (SARS) can mask the onset of subsequent neurologic complications, making their timely recognition harder. A brain disorder was in fact suspected in our patient only after discontinuing sedation, highlighting the clinical issue of whether and, if so, when to consider SARS-CoV-2 related neurological complications during prolonged periods of sedation and intubation.

Positivity of PET, but not MRI, in our patient also raises the question of which tools to use for a timely diagnosis, underlining the decisive role of molecular imaging in MRI-negative cases.

DISCLOSURE

No potential conflicts of interest relevant to this article exist.

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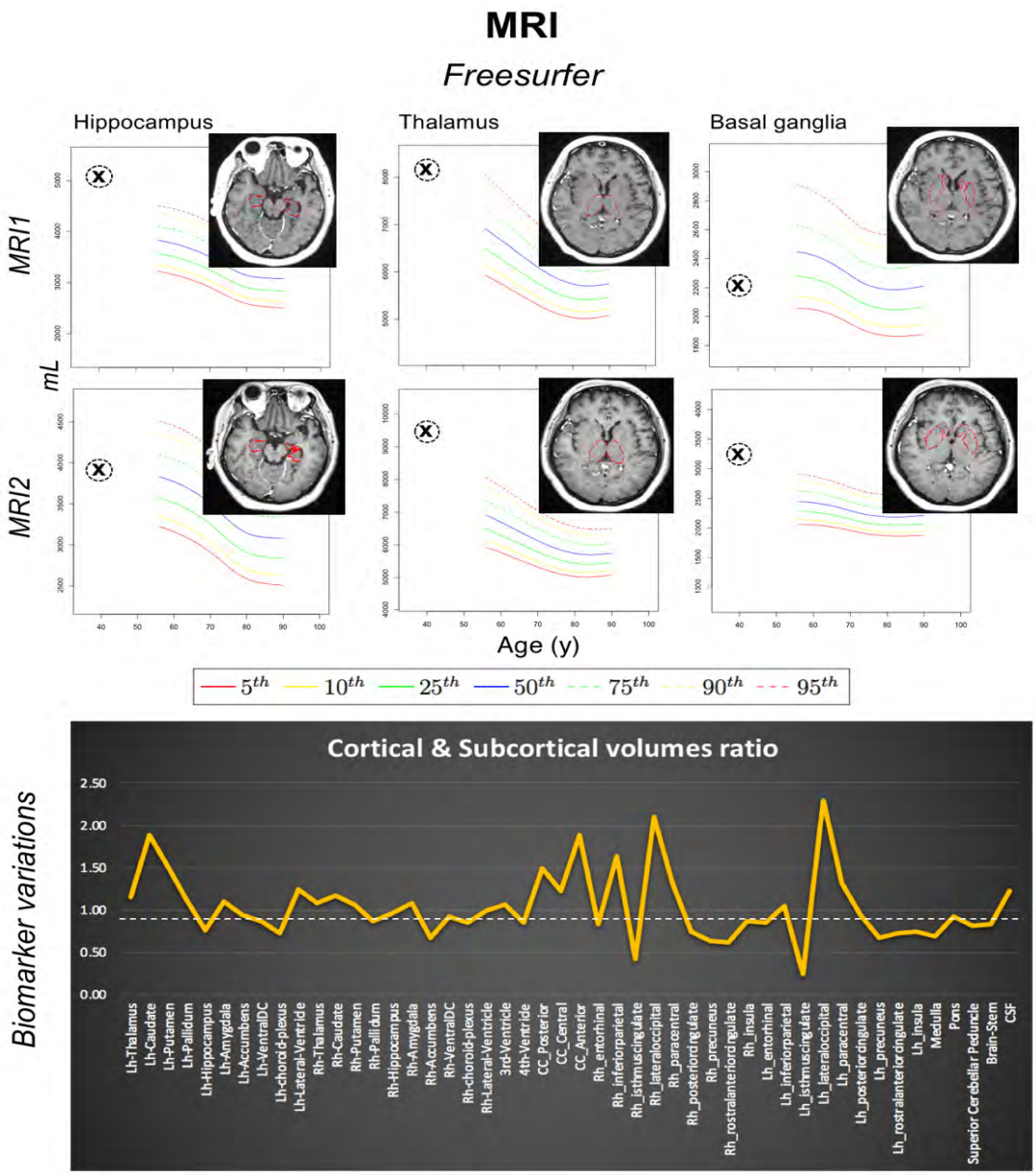
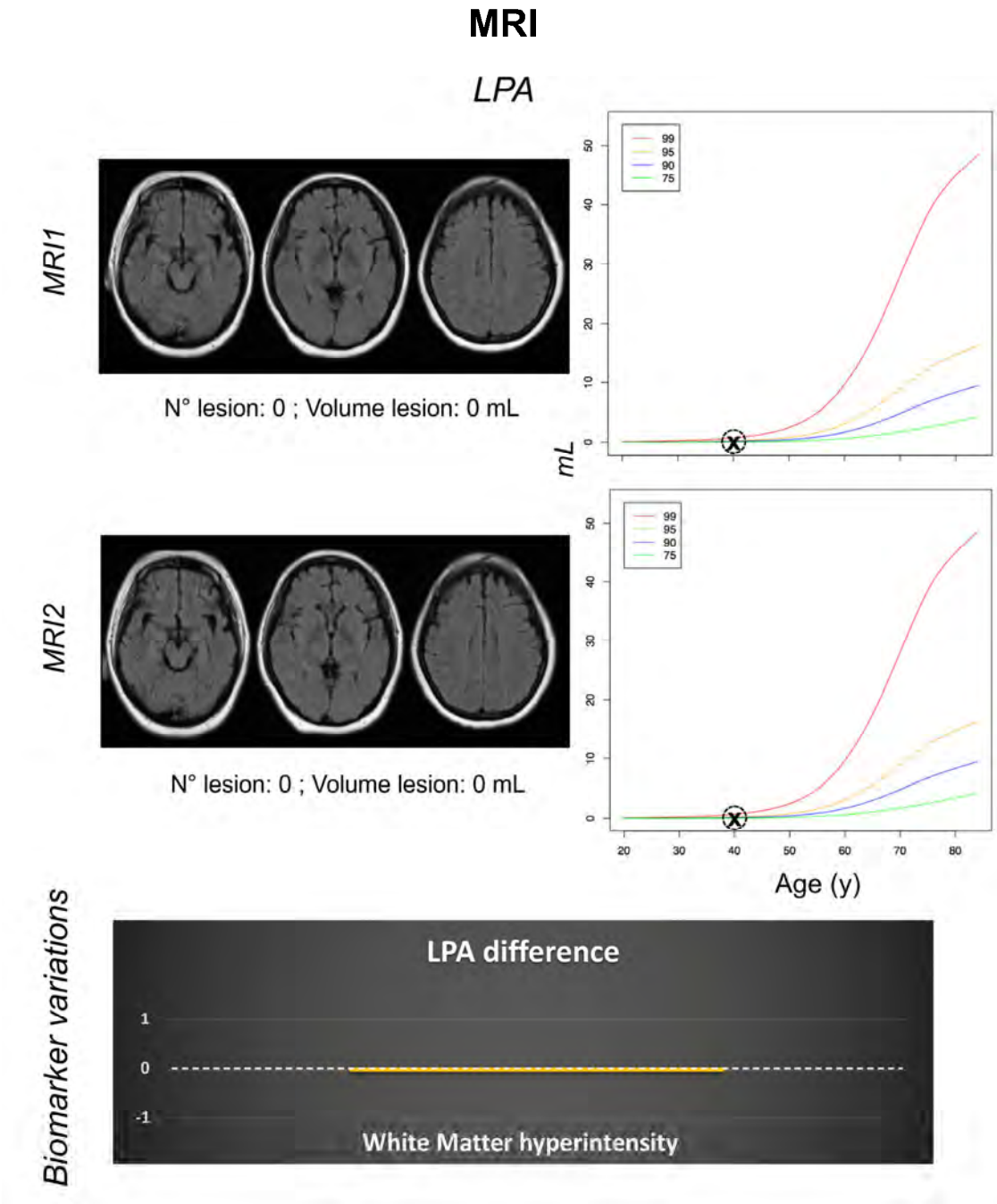
FIGURE 1



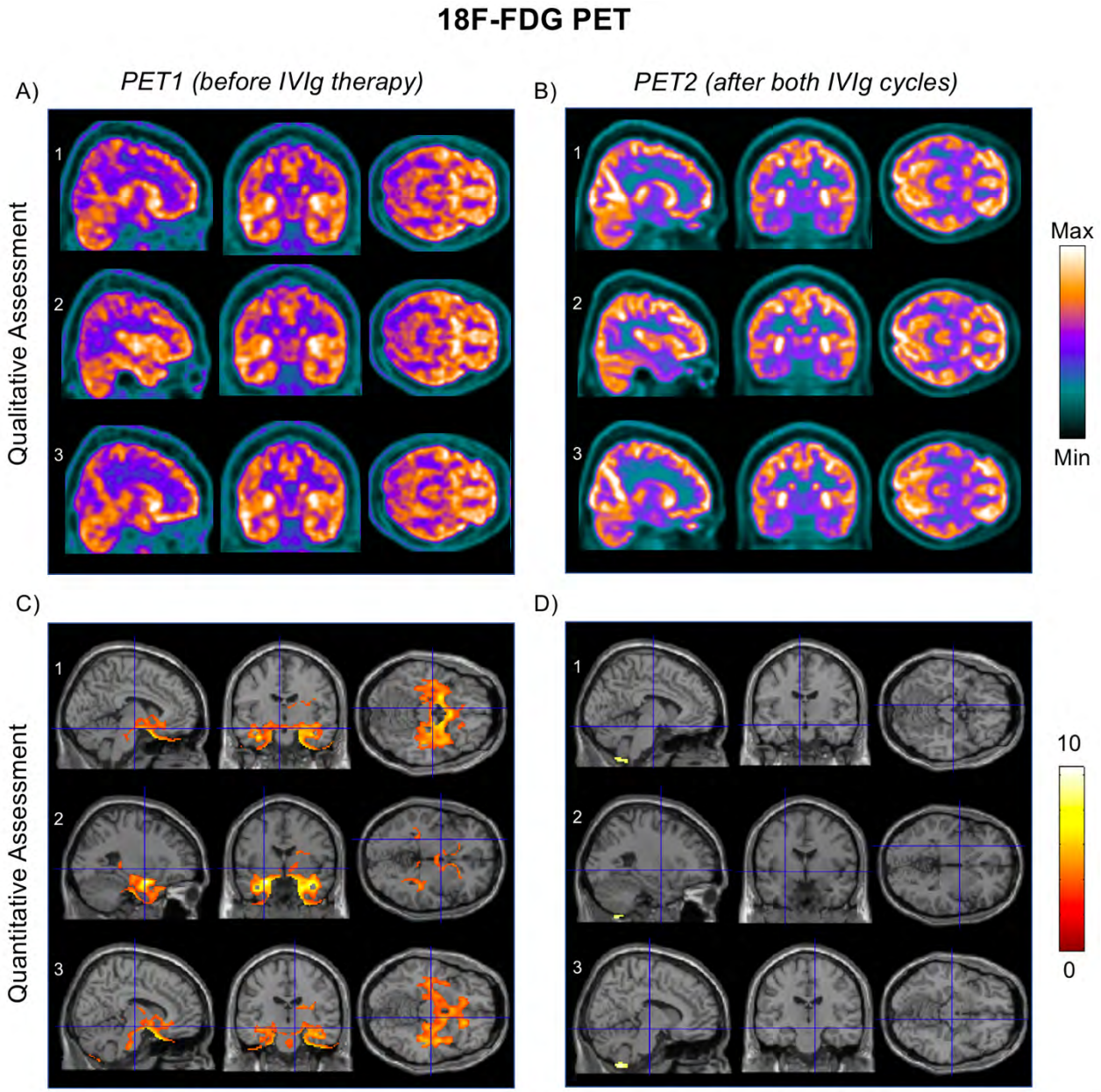
Both MRI1 (day 16) and MRI2 (day 30) were performed before IVIg therapy. T13D volumetric scans were processed with Freesurfer via neuGRID platform (https://www.neugrid2.eu). Freesurfer percentiles were derived from 532 healthy controls (age range: 55-90 years; mean and standard deviation: 73.59 +/- 6.29 years). No gray matter volume loss was detected. However, as shown in the "Biomarker variations" graph, volumes of most subcortical regions, including amygdala, thalami, and basal ganglia, were on average 10% greater at the second time point, possibly reflecting greater edema associated with the inflammatory process. Cortical regions showed a less homogeneous pattern but, overall, mean cortical volumes at the two time points were of similar magnitude.

FIGURE 2



Both MRI1 (day 16) and MRI2 (day 30) were performed before IVIg therapy. Axial 2D Flair scans were processed with Lesion Prediction Algorithm (LPA) via neuGRID platform. LPA percentiles were computed from 629 control subjects (age range: 20-90 years; mean and standard deviation: 49.82 +/- 14.63 years). No white matter hyperintensities were detected.

FIGURE 3

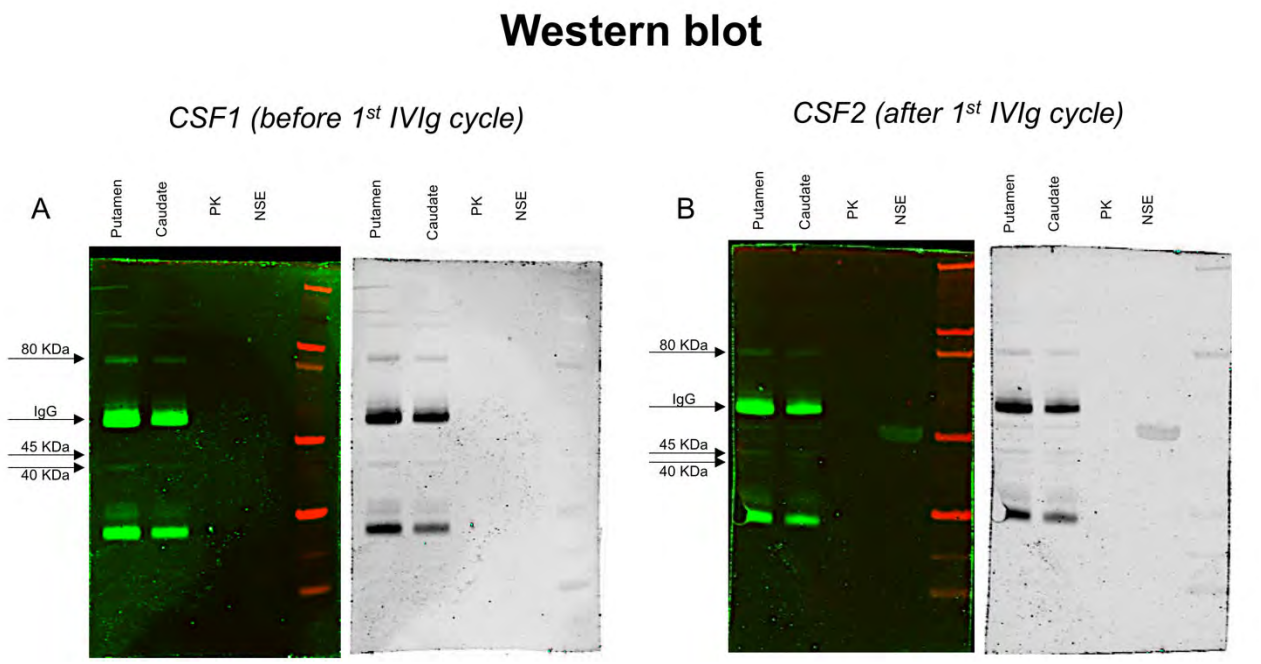


Panels A and C (PET1 - day 38 - closed eyes condition): hypermetabolism in mesial temporal lobes and subthalamic nuclei on both qualitative and quantitative (statistical parametric mapping, SPM12) assessment.

Panels B and D (PET2 - day 143 – open eyes condition): areas of increased FDG uptake in the parietal-occipital cortex (due to open-eyes condition) on qualitative, but not quantitative (SPM), assessment. Mesial temporal lobes and subthalamic nuclei had normal FDG uptake at this time.

18F-FDG PET images (panel A, B) are expressed as total effective counts. Statistical parametric maps are superimposed on the T1 template image in the ICBM152 space describing the brain activation by color-coding voxels whose t-values exceed the threshold for significance ($p<0.001$, extend threshold of 100 voxel, grand mean scaled value equal to 6.5 and proportional normalization). SPM12 normative dataset consisted of 53 healthy controls (age range: 20-82 years; mean and standard deviation: 59.08 +/- 10.55 years). Images are shown in neurological convention.

FIGURE 4



Western blot analyses of the total protein extract from human putamen and caudate brain regions (lanes 1 and 2), recombinant human Pyruvate-Kinase protein (lane 3), and recombinant human Neuron-Specific-Enolase protein (lane 4). Patient's CSF (Panel A and B) identifies bands with molecular weight of 40, 45, and 80 kilodaltons (KDa). A weak positivity for Neuron-Specific-Enolase was detected only in the post-IVIg sample (Panel B, lane 4).

PART 2

FINAL DIAGNOSIS

Our final diagnosis was immune-mediated, SARS-CoV-2-related, encephalitis. Other potential explanatory causes (e.g., paraneoplastic/autoimmune brain disorders) were excluded. However, due to non-detection of virus in the CSF, this should be considered a highly probable rather than a confirmed case of SARS-CoV-2 related encephalitis. PET was decisive in revealing direct brain involvement (encephalitis) rather than a mere indirect neurological consequence of systemic disease (encephalopathy).

The table below summarizes the clinical and paraclinical findings that most contributed to clarify the clinical problem and shed light on underlying physiopathology.

Time (days)	Main symptoms/diagnostic tests	Pathogenetic/diagnostic perspectives
0	Systemic and respiratory symptoms. Positive swab analysis for SARS-CoV-2 RNA. Positive chest CT scan for interstitial pneumonitis.	SARS-CoV-2 infection
14-16	Neurologic features (confusion, agitation). Normal MRI. Normal cellularity and protein content in CSF.	Indirect neurologic effects of systemic disease?
15-16	Neurologic features (seizures). Slow EEG, with epileptiform discharges. CSF RT-PCR negativity for SARS-CoV-2, but positivity for anti-SARS-CoV-2 antibodies.	Or direct brain involvement?
15	Negative CSF analysis for neurotropic viruses (herpes simplex-1, herpes simplex-2, human herpes virus-6, varicella-zoster, Epstein-Barr, cytomegalovirus). Negative search for antibodies directed against intracellular onconeural (Ma1, Ma2, Hu, Ri, Yo, CV2) or cell surface/synaptic antigens (N-Methyl-D-aspartate receptor, α-amino-3hydroxy-5-methyl-4-isoxazolepropionic acid receptor, γ-aminobutyric acid-A receptor, γ-aminobutyric acid-B receptor, contactine-associated proteinlike 2, leucin-rich glioma inactivated 1).	Exclusion of common infectious or paraneoplastic/autoimmune CNS disorders
38	Limbic and extra-limbic hypermetabolism on 18F-FDG PET.	Likely direct brain involvement
82	Neurologic features (parkinsonism). CSF positivity for anti-basal ganglia antibodies.	Direct brain involvement of likely immune-mediated etiology
143	Post-IVIg normalization of metabolism on 18F-FDG PET	Full recovery after immune-modulatory treatment, further supporting the hypothesis of an immune-mediated etiology

The absence of the virus in the CSF seems to indirectly support the hypothesis of an immune-mediated etiology. However, in light of suboptimal sensitivity of the PCR-based method for SARS-CoV-2, failing to identify the virus in the CSF is not sufficient to discard a direct viral infection of the CNS. Positivity for anti-SARS-CoV-2 IgG antibodies in the CSF is also of

uncertain interpretation, potentially indicating either viral CNS penetration with subsequent intrathecal antibody production or passage of peripherally generated antibodies across blood-brain barrier breakdowns induced by systemic infection. In addition to the direct CNS infection or, alternatively, the immune activation induced by the virus without CNS invasion, there is a third pathogenetic hypothesis that combines these two, according to which a neurotropic virus that has entered the CNS can activate a post-infectious, immune-mediated, encephalitic process. Herpes simplex virus 1 has for example been described as a potential trigger for the development of anti-N-methyl-D-aspartate receptor auto-immune encephalitis within few weeks after CNS infection. However, this mechanism of action is doubtfully applicable to SARS-CoV-2, because this virus, unlike herpes simplex virus 1, is not confirmed to have neuroinvasive potential.

Regardless of whether or not SARS-CoV-2 may have previously invaded the CNS, there are several considerations that, in our patient, argue in favor of a post-infectious, immune-mediated, encephalitic process, including the three-week interval from onset of systemic symptoms to development of neurologic manifestations, the site of PET abnormalities, the detection of anti-basal ganglia antibodies, and the prompt benefit from IVIg therapy.

Although the pathogenesis of most SARS-CoV-2 related complications has not yet been fully elucidated, some authors have proposed an excessive and uncontrolled immune response with massive release of cytokines (the so-called “cytokine storm”) as a possible additional mechanism of organ damage (*4*). The CSF cytokine profile of our patient, characterized by a markedly concentration of pro-inflammatory cytokines with subsequent reduction after IVIg treatment, supports a contribution of hyperinflammatory dysregulation to pathogenic events underlying SARS-CoV-2 neurological complications.

Although movement disorders have rarely been reported in the SARS-CoV-2 context, our patient showed dyskinesias and parkinsonism, both occurring relatively late in the disease course. Due to concurrent use of haloperidol, it is hard to determine if the development of parkinsonism was predominantly drug-induced or, conversely, haloperidol only influenced its persistence. Likewise, it is difficult to discern what most contributed to its disappearance, whether the impact of the second IVIg cycle or haloperidol withdrawal. Detection of immunoreactivity against striatal antigens is however a strong argument in favor of spontaneous parkinsonism, in line with the results of a recent clinic-radiological series of neurologic subjects with SARS-CoV-2 infection (*5*).

Remarkably, normality of MRI and conventional CSF analyses indicates that classical investigations might be insufficient to reveal the presence and the extent of cerebral involvement in SARS-CoV-2 related encephalitis and, as in our case, 18F-FDG PET could be a more accurate diagnostic option. The present study also highlights the potential utility of 18F-FDG PET for follow-up assessment, to better monitor the status of disease and the impact of immunomodulatory treatment.

CONCLUSION

This study emphasizes the diagnostic role of 18F-FDG PET in an MRI-negative case of SARS-CoV-2 related encephalitis and the still underreported therapeutic value of IVIg in this context.