

Single Case – General Neurology

Electroencephalographic Abnormalities in a Patient Suffering from Long-Term Neuropsychological Complications following SARS-CoV-2 Infection

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Keywords

Long COVID · Neuropsychological disturbances · Apathy · EEG

Abstract

Introduction: Emotional apathy has recently been identified as a common symptom of long COVID. While recent meta-analyses have demonstrated generalized EEG slowing with the emergence of delta rhythms in patients hospitalized for severe SARS-CoV-2 infection, no EEG study or dopamine transporter scintigraphy (DaTSCAN) has been performed in patients with long COVID presenting with apathy. The objective of this case report was to explore the pathophysiology of neuropsychological symptoms in long COVID. **Case Presentation:** A 47-year-old patient who developed a long COVID with prominent apathy following an initially clinically mild SARS-CoV-2 infection underwent neuropsychological assessment, cerebral MRI, DaTSCAN, and resting-state high-density EEG 7 months after SARS-CoV-2 infection. The EEG data were compared to those of 21 healthy participants. The patient presented with apathy, cognitive difficulties with dysexecutive syndrome, moderate attentional and verbal episodic memory disturbances, and resolution of premorbid mild gaming disorder, mild mood disturbances, and sleep disturbances. His MRI and DaTSCAN were unremarkable. EEG revealed a complex pattern of oscillatory abnormalities compared to the control group, with

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a strong increase in whole-scalp delta and beta band activity, as well as a decrease in alpha band activity. Overall, these effects were more prominent in the frontal-central-temporal region.

Conclusion: These results suggest widespread changes in EEG oscillatory patterns in a patient with long COVID characterized by neuropsychological complications with prominent apathy. Despite the inherent limitations of a case report, these results suggest dysfunction in the cortical networks involved in motivation and emotion.

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Introduction

The SARS-CoV-2 infection can lead to long-term neurological and neuropsychological complications [1]. Symptoms of long COVID are highly variable and include apathy, fatigue, hyposmia, depression, sleep disturbances, headache, and cognitive difficulties [2]. A high prevalence of emotional apathy (i.e., the ability to associate emotional value with ongoing behavior) has been described [3].

EEG abnormalities in SARS-CoV-2 patients presenting with neurological and neuropsychological complications have been mainly explored in the acute setting, in patients referred to EEG for altered mental status, poor arousal and responsiveness, or suspicion of seizures [4, 5]. Recent studies have suggested a link between long COVID syndrome's neuropsychological symptoms such as fatigue, brain fog or cognitive impairment, and delta-band resting-state power and connectivity [6–8]. Machine learning techniques analyzing resting-state EEG can differentiate long COVID patients with brain fog from controls with only 60–70% efficiency, highlighting the need for further EEG investigations in this domain [9].

Furthermore, to the best of our knowledge, no EEG investigations have been conducted in patients with a long COVID presenting mainly with emotional apathy. Here, we describe the EEG changes observed in a patient who developed a long COVID with prominent emotional and executive apathy.

Case Report

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000535241>).

Study Population

Patient

A 47-year-old married maintenance worker with a history of mild SARS-CoV-2 infection 7 months prior (in March 2020) and a mild gaming disorder since adolescence was referred for symptoms suggestive of a long COVID.

Healthy Controls

Twenty-one healthy controls (HCs) participating in a study (EC-2017-01852) gathering neurological status, structural MRI, high-density EEG, and neuropsychological data were included. Controls did not present with any symptoms of apathy, cognitive impairment, psychiatric disorders, or drug addiction.

Procedure

The patient underwent (1) a neuropsychological examination, including an assessment of apathy with the Dimensional Apathy Scale (DAS) [10], anxiety with the State-Trait Anxiety Inventory for Adults (STAI), depression with the Beck Depression Inventory II (BDI-II), impulsivity with the UPPS Impulsive Behavior Scale, and the global cognitive status by the Montreal Cognitive Assessment (MOCA); (2) a neurological examination; (3) EEG recording; (4) brain MRI; and (5) a DaTSCAN in order to see if apathy was related to dopaminergic denervation. The patient was followed up neuropsychologically at 9 and 12 months post-SARS-CoV-2 infection. The HCs underwent similar testing, except for DaTSCAN.

EEG Data Acquisition

All participants performed a 6-min eyes-closed resting-state high-density EEG (online suppl. material).

EEG Data Processing and Analyses

After classical EEG preprocessing (online suppl. material), spectral resting-state high-density EEG differences between patients and HCs were assessed using a single Hanning taper spectral transformation (online suppl. Fig). A data-driven clustering method allowed the determination of topographic patterns of spectral dissociation between patients and HCs. After dimension reduction, topographical clusters were calculated (online suppl. material). The oscillatory pattern observed in each cluster was characterized using a nonparametric Monte Carlo test performed using custom MATLAB scripts. A statistical p value was set at $p < 0.01$ (after FDR correction [11]).

Results

Seven months prior to the study, the patient presented with mild SARS-CoV-2 infection with fever, myalgia, difficulty breathing without hypoxemia, loss of motivation, and disappearance of addiction to video games. Long-lasting symptoms persisted, with an impairment of his motivation, leading to a significant impact on his activities of daily living. The patient also complained of sleep maintenance insomnia, fatigue, difficulty remembering things, and breathlessness. The patient did not report any seizures following SARS-CoV-2 infection, nor did he present any history of seizures prior to infection.

Table 1 presents the demographic and clinical characteristics of the study participants. Neurological examination was unremarkable in HCs. Additional clinical and demographic details of the HC population are presented in online supplementary material 5.

Neuropsychological Examination

Table 2 presents the results. The first neuropsychological assessment performed 7 months after SARS-CoV-2 infection showed the presence of apathy with a total score of 34/72 on the DAS (pathological results for the emotional apathy and executive apathy subscores). The patient also presented with mild mood disturbances with no anxiety, global cognitive impairment, impulse-control dysfunction, or substance or behavioral addictions. There were no significant differences in apathy ($t [19] = 0.28, p = 0.78$), fatigue ($t [19] = 1.551, p = 0.13$), anxiety ($t [19] = 0.68, p = 0.5$), or depression ($t [19] = 1.597, p = 0.13$) between pre- and postpandemic HCs.

Structural Examination

Patient's brain MRI and DaTSCAN (Fig. 1) were unremarkable.

Table 1. Demographic and clinical characteristics of the two groups of participants

	Patient	Controls
Demographics		
Participants, <i>n</i> (men)	1 (1)	21 (8)
Median age, years (Q1; Q3)	47	57 (46; 69)
Laterality	Right	Right (21/21)
Neurological and neuropsychological symptoms		
Starkstein apathy score (/42)	12	7 (5; 10)
Anxiety (STAI)		
State (/80)	28	24 (23; 27)
Trait (/80)	25	30 (28; 33)
Depression (BDI) (/63)	15	4 (3; 6)
Impulsivity (UPPS) (/180)	89	82 (77; 89)
Cognitive score MoCA (/30)	28	29 (29; 30)

Values are expressed as median (Q1; Q3) scores for the HC group. A Starkstein apathy score of $\geq 14/42$, an anxiety State-Trait Anxiety Inventory (STAI) score $\geq 50/80$ for State and $\geq 48/80$ for Trait, and a depression Beck Depression Inventory (BDI) score $\geq 21/63$ were considered to be pathological cutoff values. MoCA, Montreal Cognitive Assessment.

EEG Data

The patient's EEG did not present with any epileptiform activity. The patient showed a topographically distributed pattern of spectral differences with well-defined topographical clusters of spectral differences compared with HCs (Fig. 2).

Within the low-frequency band spectrum, a spectral increase in the delta-low theta band (2–6 Hz, $p < 0.01$, FDR corrected) was observed in the central-temporal area and occipital clusters concomitant with a decrease in the alpha band (8–12 Hz, SD, $p < 0.01$, FDR corrected) for the patient compared to HCs. A similar alpha band decrease was observed in the frontal cluster extending into the low-beta band (13–19 Hz, $p < 0.01$, FDR corrected). There was a striking difference between the frontal-central-temporal clusters and the anterior-occipital cluster 7 with the presence of an alpha peak at 10 Hz for the patient, reaching significance compared to HCs ($p < 0.01$ FDR corrected).

Within the high-frequency band spectrum, a spectral increase in the beta band (19–36 Hz) was observed in the patient compared to HCs across the scalp ($p < 0.01$, FDR corrected). However, the frequency extent of this effect varied depending on the scalp location, with the largest frequency extent in the central-temporal clusters ($p < 0.01$, FDR corrected). The frequency of this effect was greatly reduced in frontal cluster C1 (25–31 Hz, $p < 0.01$, FDR corrected), right and anterior occipital clusters C6 and C7, and almost abolished in left occipital cluster C5 (SD, $p < 0.01$, FDR corrected). Finally, a spectral decrease in the low-gamma band was observed in the patient compared to the HCs for frontotemporal clusters. A similar low-gamma effect was observed above 43 Hz for clusters C7, C5, and C2.

Follow-Up

A neuropsychological assessment performed 9 months after the infection showed the persistence of emotional apathy, the presence of a dysexecutive syndrome (difficulties in inhibition, shifting, verbal fluency, and processing speed), and moderate attentional and

Table 2. Results of the patient's neuropsychological evaluations

Psychiatric questionnaires	7 months after COVID-19 infection	9 months after COVID-19 infection	12 months after COVID-19 infection
Apathy assessment			
Dimensional Apathy Scale (DAS)			
Total score (/72)	34		11
Executive apathy subscore (/24)	16		8
Emotional apathy subscore (/24)	15		1
Cognitive initiation subscore (/24)	3		2
Apathy Motivation Index (AMI)			
Total score (mean score)		1.61	
Behavioral apathy (mean score)		1.50	
Social apathy (mean score)		1.50	
Emotional apathy (mean score)		1.83	
Beck Depression Inventory (BDI) (/63)	15	8	9
State-Trait Anxiety Inventory (STAI)			
State subitem (/80)	28	36	27
Trait subitem (/80)	25	27	33
Posttraumatic Stress Disorder Checklist for DSM V (PCL-5) (/80)		23	
French version of the fatigue impact scale in multiple sclerosis (EMIF – SEP)			
Total score (/168)		87	
Sleep			
Epworth Sleepiness Scale (/24)		12	
Insomnia State Index (ISI) (/28)		15	
Mania – Goldberg inventory (/66)		7	
Dissociative Experiences Scale (DES) (mean score)		1.43	
Emotion Contagion Scale (ECS) (/60)		25	
Emotion Regulation Questionnaire (ERQ) (/70)		44	
Cognitive complaints questionnaire (QPC) (/10)		8	
Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)			
Tobacco (/34)	0		
Alcohol (/34)	4		
Cannabis (/34)	0		
Amphetamine (/34)	0		
Inhalants (/34)	0		
Sedatives (/34)	0		
Hallucinogens (/34)	0		
Opioids (/34)	0		

Table 2 (continued)

Psychiatric questionnaires	7 months after COVID-19 infection	9 months after COVID-19 infection	12 months after COVID-19 infection
Attention – TAP			
Phasic alertness			
Without warning sound – reaction time		222'	
Without warning sound – SD of reaction time		27'	
With warning sound – reaction time		241'	
With warning sound – SD of reaction time		40'	
Divided attention			
Item omissions		1	
False alarm		3	
Sustained attention test			
Item omissions		22	
False alarm		46	
Memory			
Verbal episodic memory – Grober & Buschke (FR/CR 16)			
Immediate recall (/16)		16	
Sum of 3 free recalls (/48)		27	
Sum of 3 total recalls (/48)		42	
Delayed free recall (/16)		11	
Delayed total recall (/16)		14	
Visuospatial episodic memory – Rey figure			
Copy time		169'	
Score (/36)		34	
Immediate recall (/36)		20	
Delayed recall (/36)		31	
Verbal short-term memory – MEM III spans			
		9	
Visuospatial short-term memory – WAIS IV spans			
		7	
Executive functions			
Inhibition – Stroop GREFEX			
Interference – time		185'	
Interference – errors		3	
Interference/naming – score		62	
Mental flexibility – TMT GREFEX			
TMT B – time		80'	
TMT B – errors		2	
TMT B – perseverations		0	
TMT B/A – score		53	

Table 2 (continued)

Psychiatric questionnaires	7 months after COVID-19 infection	9 months after COVID-19 infection	12 months after COVID-19 infection
Verbal working memory – MEM III		7	
Visuospatial working memory – WAIS IV		6	
Verbal fluency (2') – GREFEX			
Literal		13	
Categorical		18	
Instrumental functions			
Language – BECLA			
Semantic image matching (/20)		17	
Semantic word matching (/20)		18	
Object and action image naming (/20)		20	
Word retention (/15)		15	
Nonword repetition (/10)		10	
Ideomotor praxis – praxis from Moroni			
Symbolic gestures (/5)		5	
Action pantomimes (/10)		9	
Meaningless gestures (/8)		8	
Object perception – VOSP			
Fragmented letters (/20)		19	
Object decision (/20)		13	
Spatial perception – VOSP			
Number localization (/10)		8	
Cubic counting (/10)		8	
Logical reasoning – WAIS IV			
Puzzle		7	
Matrix		9	
Emotion recognition			
Emotion recognition task (no norms) – GERT (/42)		17	

For psychiatric questionnaires, scores in bold are above the pathological threshold. For neuropsychological testing, scores in bold are substandard (< percentile 5; < T-score of 33.6; < Z-score of -1.60). Dimensional Apathy Scale cutoffs: apathy is significant if the total score is $\geq 29/72$ and if subscores are $\geq 10/24$ for executive apathy, $\geq 11/24$ for emotional apathy, and $\geq 14/24$ for initiation apathy. Beck Depression Inventory cutoffs: mild mood disturbance if the score is within the range of 11–16/63, borderline clinical depression if the score is within the range of 17–20/63, moderate depression if the score is within the range of 21–30/63, severe depression if the score is within the range of 31–40/63, and extreme depression if the score is $>40/63$. ASSIST is a questionnaire that screens for the level of problem or risky substance use in adults. EMIF-SEP: the average for the EMIF-SEP is calculated on a score of 100%. In our case, the patient had a fatigue score of 54.38%. The mean according to the literature (Debouverie et al. Multiple Sclerosis 2007) is 57.70 and SD 22.70 (percentile 25 = 46 and percentile 75 = 74), so our patient does not have a pathological score. Other calculation (standardization): Z-score of -0.14, thus in the norm.

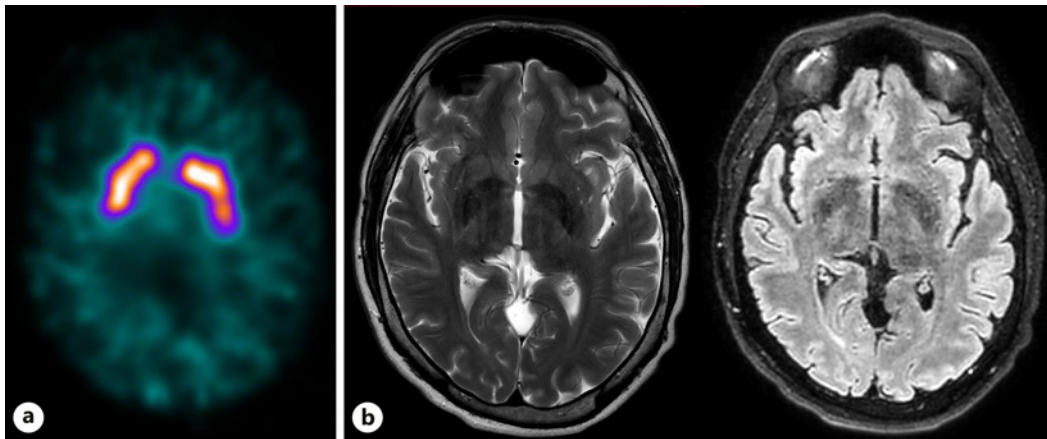


Fig. 1. Patient imaging results. **a** DaT SPECT with [123 I]FP-CIT showed a visual distribution of the radiotracer within the striatum within the norms. **b** Brain MRI. Axial T2 and FLAIR images show the absence of brain lesions, leukoencephalopathy, or cerebral atrophy.

verbal episodic memory disturbances with slowness in encoding and difficulties in storage (Table 2). While the patient did not display a pathological level of fatigue, the insomnia and daytime sleepiness scores were pathological. Depression scores were normalized. There were no signs of posttraumatic stress disorder. A neuropsychological assessment performed 1 year after the SARS-CoV-2 infection showed resolution of apathy and mood disturbances (Table 2).

Discussion

Our study reports widespread oscillatory abnormalities in a patient suffering from long-term post-SARS-CoV-2 neuropsychological complications with prominent emotional and executive apathy. Compared to HCs, our patient presented with diffuse EEG slowing predominantly in the frontal-central-temporal regions, with an increase in delta and theta band activity, as well as a decrease in alpha band activity. An increase in beta-band activity was also observed in the central-temporal regions.

Our patient's EEG findings were close to the EEG abnormalities found in patients in the context of a severe acute SARS-CoV-2 infection or in those recently recovering from a severe form of SARS-CoV-2, in which generalized or focal EEG slowing with abnormal delta prominence and decreased alpha activity, epileptiform abnormalities, and periodic discharges have been reported [4, 5].

The delta- and alpha-band modifications observed in our patient might represent persistent brain dysfunction secondary to SARS-CoV-2 infection. Indeed, a previous study observed a reduction in frontal activity and EEG complexity at rest 6–12 months post-mild-SARS-CoV-2 infection [12]. Interestingly, several lines of evidence link delta-band and theta activity increase to acute and chronic inflammatory state secondary to infectious diseases [13–17]. Delta band activity increases were also observed in mice following systemic administration of lipopolysaccharide (i.e., bacterial endotoxin) and correlated with the cortical level of the proinflammatory cytokine IL6 [18]. An increase in delta and theta oscillations was also observed in chronic inflammation models, such as chronic knee osteoarthritis, and related with pain, depression, and poor cognition [19]. As long COVID is associated with viral-load reactivation and chronic inflammatory processes, these mechanisms might play a role in the results we obtained in the current study [20, 21]. Cognitive evaluation

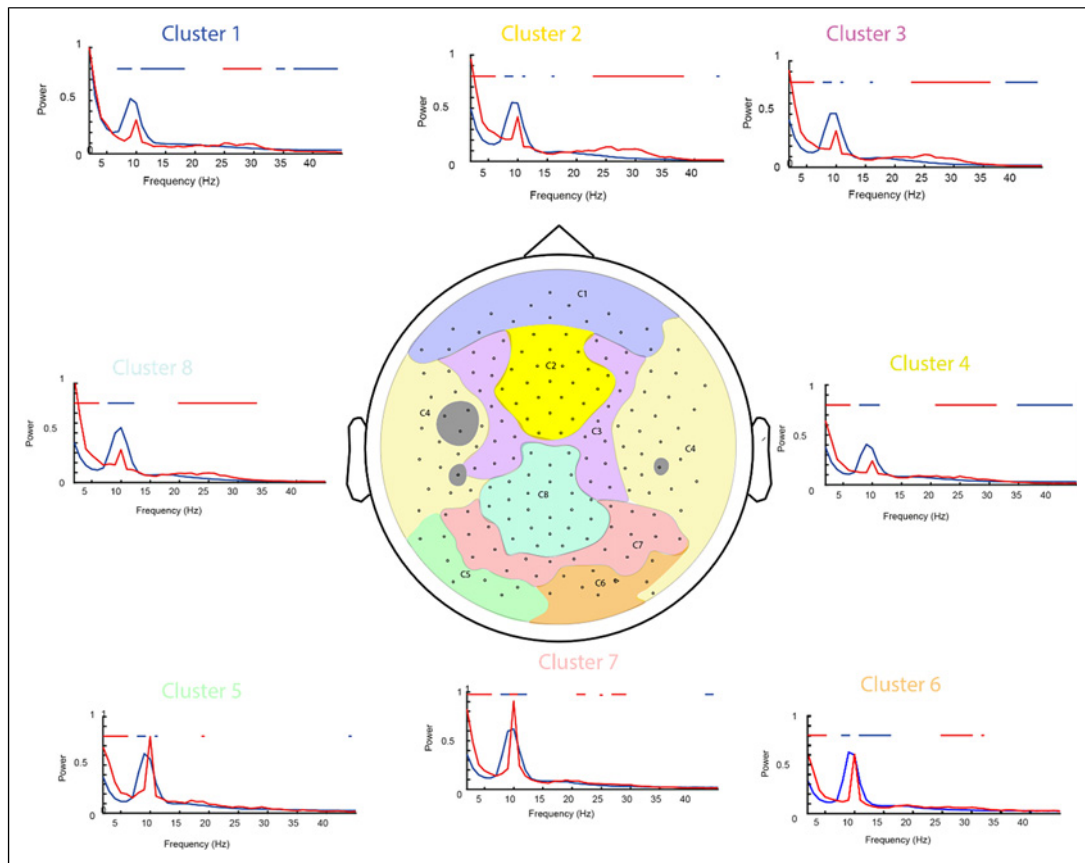


Fig. 2. EEG spectrograms in several topographical clusters in the mild-COVID patient (in red) and a HC population (in blue). Compared to HCs, the patient presented with diffuse EEG slowing predominantly in the frontal-central-temporal regions, with an increase in delta and theta band activity, as well as a decrease in alpha band activity. An increase in beta band activity was also observed in the central-temporal regions.

revealed mild but significant differences only in executive functions [12]. Interestingly, the peak of beta-band activity increase in our patient was located within the central topographical clusters. A recent study using transcranial magnetic stimulation of the primary motor cortex (M1) pointed an altered excitability and neurotransmission within M1 in patients with executive deficits following SARS-CoV-2 infection [7, 22]. As beta-band activity is a hallmark of motor and executive functions, this modification might be linked to the executive alterations observed in the current study.

The spectral modifications observed in our patient might be related to neuropsychological and cognitive deficits. Given the clinical significance of apathy, we hypothesized that the observed abnormalities reflect a functional disruption in the physiological oscillatory processing of emotional cues and motivation, thus interfering with the patient's emotional motivational system. Our patient exhibited a strong increase in delta-theta power in the frontal-central clusters in accordance with the EEG abnormalities observed in apathy in Parkinson's disease (PD) and Alzheimer's disease (AD) [23, 24]. A recent study reported depression, fatigue, and a worsening of cognitive functioning following SARS-CoV-2 infection in patients with AD and PD with dementia, suggesting some shared pathomechanisms between long COVID and dementia [25].

A previous EEG study showed a positive correlation between low-frequency band spectrum delta power and PD-associated apathy in the frontal regions [26]. Absolute theta power has also been shown to be significantly higher in the central region of apathetic patients with PD than in nonapathetic patients with PD and HCs [27]. Similarly, quantitative EEG has shown an increase in theta power in the apathetic compared to nonapathetic AD patients in the frontal and central regions [28]. There is a correlation between whole-brain alpha band EEG decreased connectivity and apathy in PD, which also provides a potential link between the apathetic symptoms and the whole-brain disruption in alpha activity observed in our patient [26]. Alpha band activity has also been linked to the processing of emotional cues in the subthalamic nucleus of PD patients [29] and scalp EEG recordings [30].

Apathy involves dopaminergic, serotonergic, cholinergic, and noradrenergic systems [23]. We did not find any evidence of a structural lesion within the reward and basal ganglia systems or in the dopaminergic pathway, which could explain the apathetic phenotype.

This study has some limitations. A case report does not allow the generalization of the current results to a larger population, nor does it infer a direct correlation between EEG markers and symptoms. The absence of “baseline” recording (pre-SARS-CoV-2 examination) does not allow to prove that the abnormalities observed were a variation from baseline. However, HCs did not present with any apathy, depression, or neuropsychological symptoms. Furthermore, our patient age was 47 years old, while the median age for our control group was 57 years old. According to EEG studies on aging, older participants display less delta and theta, some reduction in alpha, and increased beta [31]. The small magnitude of the observed effects while comparing groups with 50-year age difference (against 10 years in the current study) makes it unlikely that the results observed in our study can be fully attributed to the age difference between our two groups. Finally, the SARS-CoV-2 pandemic itself could be associated with rising levels of fatigue, depression, and anxiety, which could partly overlap with our results.

Altogether, our case suggests that a long COVID with neuropsychological disturbances impacts the functioning of the central nervous system. Emotional and motivational processes may also be affected. This report might pave the way toward more stringent cohort investigations on this population to better understand the pathophysiology of long COVID.

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Statement of Ethics

This study was approved by the Geneva Ethics Committee (EC-2017-01852). It complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. All the participants provided written informed consent. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. Written informed consent was obtained from the patient for the publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest relevant to this work to declare.

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Author Contributions

D.B.: conception, acquisition, analysis, interpretation of the work, and drafting the work. P.V., S.C.C., and V.G.: acquisition, interpretation of the work, and editing of final version of the manuscript. F.A., J.P.: interpretation of the work and editing of final version of the manuscript. P.K.: conception, interpretation of the work, and editing of final version of the manuscript. V.F.: conception, acquisition, analysis, interpretation of the work, drafting the work, and editing of final version of the manuscript.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available in the article and its supplementary materials. Further inquiries can be directed to the corresponding author.

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