

Unexpected Improvement of Chronic Neurological Disease after Recovery from COVID-19 Infection in Four Patients

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Abstract

During the COVID-19 pandemic, physicians actively searched for adverse neurological complications or coagulopathy-related strokes, but no protective effects were yet reported. We hereby describe our observations at a Geriatrics / Neurology facility on a range of neurological disorders encountered among COVID-19 patients followed for disabling neurological disease (degenerative or post traumatic dementia). We observed a very significant clinical improvement in 4 patients aged 43 to 78, who were in nursing skills home or at home and followed up for a disabling neurological disease for 2 to 5 years. They were affected by COVID-19 between March and October 2020.

The first patient had a severe frontotemporal dementia with motor neuron disease and was confined to the bed and the armchair. He no longer had any voluntary motor skills. His dementia was severe with long lasting delusions and hallucinations, memory loss, and disorientation. While suffering from COVID-19 lung disease in April, he regained a voluntary motor function of the limbs. His cognitive status improved considerably, with the normalization of the mental mini-test and normal communication. He is now able to walk with a walker 100 meters long.

The second patient had a very severe head injury, after falling from a height of 5 meters, with cerebellar syndrome, aphasia, massive frontal lobe syndrome and behavioral disorders. He was confined to armchair. Suffering from severe COVID-19 lung disease in April, he was not hospitalized but received intensive care. He gradually showed an overall neurological improvement. He now walks alone for a few steps; his social behavior has improved considerably, and aggressive behavior has totally disappeared.

The third patient had a severe cerebral anoxia after attempted suicide by hanging. He was confined to armchair, with catatonia, related to lentiform nucleus lesions. Two months after a COVID-19 infection, his walking improved, and the catatonia disappeared. In January 2021, he normally walks more than 500 meters daily.

The fourth patient is a 78-year-old woman, who has been followed for 5 years for probable cortico-basal degeneration and suffered a severe COVID-19 lung disease in October. While recovering from COVID-19 pneumonia, she showed improvement in the motor skills of the limb previously affected.

Neurological improvement in these 4 patients was observed 2 to 4 weeks after COVID infection and was maintained over the long term but mild cognitive worsening was observed in 2 cases. We hypothesize that antibodies related to COVID-19 infection might induce an activation of microglial cells. The neurological effects of COVID vaccination should be analyzed in patients with cerebral diseases, particularly tauopathy (neurodegenerative diseases involving the aggregation of tau protein into neurofibrillary tangles in the human brain), and anoxic or traumatic encephalopathy.

Keywords: Covid-19; Tauopathy; Post traumatic; Anoxic brain

Introduction

Coronavirus Disease (COVID-19), spreading from China, was observed in Northern France and Belgium in early 2020. However, the first epidemic period started in March 2020, and affected thousands of patients with neurological comorbidity. Among all hospitalized patients for COVID-19, 8% had preexisting neurologic illness [1]. Moreover, several neurological complications of COVID-19 have been reported; from benign headaches, olfactory loss and dysgeusia, to stroke, encephalitis or meningo-myelitis [2]. Human respiratory viruses have proven their potential neuroinvasive and neurotropic effects with major neuropathological consequences [3]. Explicitly, H1N1 influenza virus with 1917 pandemic was responsible for lethargic encephalitis, and delayed, long-lasting parkinsonism [3,4]. Jang et al. [5] showed that influenza virus activates the immune system in the brain. Neurological complications of COVID-19 suggest that the virus can infect the peripheral nervous system (PNS) and/or the central nervous system (CNS) either by direct infection of nerve endings in the tissues and using axonal transport machinery to gain access to the CNS, or by infecting cells of the circulatory system that ultimately carry the infection through the blood-brain barrier (BBB) into the CNS [6].

A careful review of published literature using query “SARS-CoV-2 OR Covid-19 on PubMed (90,916 results in PubMed consulted January 10, 2021; <https://pubmed.ncbi.nlm.nih.gov>) showed that none of the publications addressed the possibility of an improvement of neurological chronic disease days or weeks after COVID-19 pneumonia. However, MRI study performed 3 months after COVID-19 recovery showed a significant increase of gray matter volumes (GMV) in olfactory cortices, hippocampi, insulas, left Rolandic operculum, left Heschl's gyrus and right cingulate gyrus, in comparison with non-COVID-19 volunteers, and these events were interpreted as being suggestive of a possible disruption to micro-structural and functional brain integrity in the recovery stages of COVID-19 [7]. We hereby report about an unexpected improvement of chronic neurological disease after Covid-19 infection in four patients.

Patients and Methods

Among 198 patients with close neurological follow up, with clinical examination at least every 3 months (in relation to the severity of their neurological illness and/or behavior troubles), 48 (24%) had confirmed COVID-19 infection according to the WHO case classification. Among these patients, 14 were women and 34 were men. All the patients except one (waiting for a nursing home admission) were living in nursing skills home, for neurological and/or psychiatric disorders, associated with cognitive impairment, and/or behavior troubles. The mean age of the whole group was 41.25 years (from 19 to 78, SD: 14). The mean age of patients affected by COVID-19 was 41.3 years (from 20 to 78, SD 15). Only 1 patient died. Among these patients with clinical symptoms of pneumonia and positive real-time reverse transcriptase– polymerase chain reaction (RT-PCR) for SARS-CoV-2, 4 patients with disabling neurological disease showed spectacular improvement of neurological or behavioral symptoms, 15 to 60 days after COVID-19 diagnosis.

The Table 1 summarizes details about their age, initial neurological conditions, follow up duration, date of COVID diagnosis, duration of oxygen requirement, delay for clinical improvement, and evaluation of disability before and after COVID-19, with mini- mental-status, Cohen-Mansfield scale [8], Barthel score [9]. Cohen-Mansfield lower score is 29 in persons without any behavior disorders and can reach 203 in patients with permanent aggressive behavior and agitation. Catatonia evaluation with Bush and Francis scale [10] was completed for patient 3.

Features	Case 1	Case 2	Case 3	Case 4
Chronic disease	FT dementia	Traumatic brain	Anoxic brain	Corticobasal degeneration
Predominant disability	Walking apraxia	Behavior disorders	Catatonia	Arm apraxia
Cognitive impairment	severe	severe	severe	moderate
Disease duration	5 yrs.	3 yrs.	15 yrs.	3 yrs.
Follow up duration	5 yrs.	1 yrs.	3 yrs.	3 yrs.
COVID-19 onset	March 2020	April 2020	April 2020	October 2020
Date of positive COVID-19 PCR (m/d/y)	04/08/2020	04/17/2020	04/17/2020	10/23/2020
Oxygen requirement	14 days	7 days	None	24 days
Pneumonia related to COVID-19	Moderate	Moderate	Mild	Severe
Hospitalization duration	7 days	0 days	0 days	47 days
Lymphocytes count during COVID-19	363/ μ l	1380/ μ l	2600/ μ l	632/ μ l
Blood COVID-19 antibodies	Positive	Positive	Positive	Positive
Delay of improvement after COVID-19 diagnosis	15 days	20 days	30 days	15 days
Major features of improvement	Motor and cognitive	Behavior	Behavior	Apraxia improvement
MMS score before COVID-19 (/30)	7	0	0	20
MMS score after COVID (/30)	30	0	0	23
Cohen Mansfield score before COVID-19	41	124	38	37
Cohen Mansfield score after COVID-19	29	34	38	29
Barthel score before COVID-19	0	0	0	40
Barthel score after COVID-19	65	15	20	45

Table 1: A summary of details of the 4 patients showing unexpected improvement of chronic neurological disease after recovery from COVID-19 infection

Case Reports

Case 1

This 74-year-old man had bipolar disorder occurring when he was 23 years old. He developed apathy when he was 67 years old, and later rest and postural tremor at the age of 69 years. At this step, psychotropic drugs were stopped, particularly cyamemazine and clomipramine, without side effects on mood. Six months later, he had difficulty for car driving, and showed walking disorders with falls. As the walking apraxia worsened, with backward falls, he developed pyramidal syndrome, severe axial parkinsonism and intentional arm tremor. Simultaneously, we observed cognitive decline, with hallucinations, delusions, disorientation and memory loss. Brain MRI showed diffuse brain atrophy. Spinal MRI was normal. Positron emission tomography (PET) combined with computed tomography (CT) with ^{18}F -fluorodeoxyglucose (^{18}F -FDG-PET/CT) of the brain showed diffuse cortical hypometabolism, predominant in the associative cortex of the left hemisphere. Dopamine-transporter single-photon emission computed tomography (DAT-SPECT) was normal. Cerebrospinal fluid (CSF) analysis was normal, with negative markers for Creutzfeldt-Jakob disease, as well as markers for paraneoplastic syndrome. Electromyography revealed associated motor neuron disease, suggestive of associated amyotrophic lateral sclerosis syndrome (ALS). The cognitive decline with frontal lobe syndrome (apathy, behavior trouble), psychosis and language deficit worsened. Genetic study for frontotemporal spectrum disorder (FTSD) was negative.

We concluded the patient had sporadic FTSD, according to Amyotrophic lateral sclerosis - frontotemporal spectrum disorder (ALS-FTSD) revised criteria [11].

In December 2016, the patient was no more able to stand up and to walk. He was admitted into the nursing skills home close to Wattrelos hospital. During the following years, his condition worsened. Mini-mental-score (MMS) was 21/30 in 2016, 16/30 in 2018 and 07/30 in February 2020. He had permanent hallucinations, delusions and psychosis. Between 2017 and early 2020, he was confined on bed and armchair. He required assistance for all daily activities, including eating. The motor apraxia affected the four limbs.

He was affected by COVID-19 with fever and permanent cough at the end of March 2020. The real-time RT-PCR for SARS-CoV-2 detection was positive on April 8th, 2020. He required oxygen assistance with non-invasive ventilation, related to COVID-19 pneumopathy and was admitted in the intensive care unit. While his respiratory function improved, nurses observed that he was able to move his legs and put them over the bed rails on April 20th. After he returned to the nursing home, voluntary movements progressed, and the physiotherapist team helped him to stand up in June and to walk with a walker. The improvement of cognition, behavior and motor function was communicated by his spouse, who called Dr. Caparros-Lefebvre to visit the patient in the nursing home to witness this unexpected improvement of neurological condition, and further discuss the likely reasons. Meanwhile, the frontal lobe syndrome related to FTSD improved considerably. MMS was 27/30 in June 2020. Language was normal. Delusions and psychosis disappeared. Brain MRI was unchanged. Brain ¹⁸F-FDG-PET/CT measuring cortical metabolism revealed, by z- score, a mild improvement of cortical hypometabolism as compared to the previous assessment in 2016.

At the time of submission of this paper (January 11th 2021), the patient is able to walk with the walker 100 meters long, although under supervision because of postural instability. MMS was 30/30 in August and is back to 27/30 (3 points lost for calculation). The patient today is able to name all the nurses attending, is continent, is able to wash his upper body himself, and eats alone. His behavior is normal.

Case 2

This 58-year-old man, working as a roofer fell down from a scaffolding 5 meters high in November 2017. He had a severe head trauma, with coma (Glasgow score 3) and bilateral mydriasis. Brain Computed Tomography scanner (CT-scan) showed multiple hemorrhagic contusions located in the right frontal and temporo-occipital lobes, left frontal and temporal lobe, and both cerebellar lobes. The therapeutic sedation and invasive ventilation were continued for 1 month. During the neurological rehabilitation from March 2018 to November 2018, only the motor function was improved, and he was able to stand up and walk few meters with physical help. He fell down several times per day, because he had anosognosia regarding his cerebellar lobe syndrome. He had a global aphasia and was mute. He had a very severe frontal lobe syndrome with impulsive and aggressive behavior, disinhibition, bulimia. The COHEN-MANSFIELD score of agitation [9] was very high at 124/203, due to physical aggressivity, and global agitation. He was incontinent, and required complete assistance for eating and to wash. He was admitted in a nursing skills home in 2018. His behavior troubles were stable. Neuroleptics and anxiolytics were not effective to improve his aggressive behavior, and induced sleepiness.

In April 2020, he was affected by COVID-19 pneumonia with fever, cough, diarrhea, and a positive RT-PCR. His general condition was severely altered. He required oxygen assistance and long-lasting subcutaneous infusions at the nursing home. Twenty days after COVID-19 diagnosis, he was able to stand up alone, and to walk with a minimal assistance. Nevertheless, he fell down frequently since the cerebellar syndrome did not improve significantly. Today, the patient is able to eat on his own; the frontal lobe syndrome has radically improved; repetitive movements and aggressive behavior have disappeared; and COHEN-MANSFIELD score has improved from 124 to 34/203. With a remarkable improvement in his behavior, the patient is more socially acceptable.

Case 3

This 43-year-old man has a history of drug abuse (opioids). He attempted to commit suicide by hanging at the age of 28 years, followed by a severe post anoxic encephalopathy, with catatonic syndrome. His behavior was marked by immobility, stupor,

mutism, fixed gaze, stereotypies, mannerism, and rigidity which are typical symptoms of catatonic syndrome. He also showed unusual paroxysmal hyperactivity, during few hours or days occurring once a month, which is a common feature of this syndrome. Due to the catatonia, he was confined to bed and armchair and remained in a long-term mental health care unit of a psychiatric hospital. Brain MRI showed diffuse small hyperintensities of both lentiform nuclei and a large hyperintensity of the right frontal lobe. This frontal hyperintensity was stable in the long term and was related to anoxic brain lesions or post traumatic lesion. CSF study was normal. Polysomnographic study was normal. Several therapeutics were tried: electroconvulsive therapy, zolpidem, without significant effect. He was admitted in a nursing skills home in 2017. The catatonic syndrome was stable over years. He required assistance for all daily activities including eating. He used to urinate in unappropriated places, in front of other patients.

He was affected by COVID-19 in April 2020, with fever and diarrhea, and positive RT-PCR. His general condition was severely altered. He required long-lasting subcutaneous infusions in his nursing home.

Thirty days after he recovered from COVID-19, nurses observed an improvement of voluntary movements, and long-lasting improvement of catatonic features. Presently, he has severe hypophonia and dysarthria, but is able to walk normally. He is able to eat on his own, is more polite, and his abnormal behavior has disappeared – particularly urination facing other residents. During birthday festivities, he dances with the rhythm of music. The Bush and Francis rating scale for catatonia was completed with the nurses; the score was 34 before COVID-19 and has dropped to 22 now, in connection with improvement in several symptoms.

Case 4

This 78-year-old woman developed progressive right-hand apraxia in 2015, associated with right limb myoclonus, alien hand and parkinsonism rigidity of the right arm. She fulfilled the criteria for corticobasal degeneration [12]. Brain MRI showed frontoparietal atrophy of the left hemisphere. Brain ¹⁸F-FDG-PET/CT showed hypometabolism involving associative cortices, predominating on the left and posterior parietal cortex. As the disease progressed, she had axial parkinsonian syndrome with gait slowing and postural instability. She had a right arm dystonia. After several falls in 2019, she progressively required assistance for daily activities, including to feed. The first neuropsychological testing in 2017 showed reduced verbal fluency. Repeated cognitive testing showed dysexecutive syndrome with altered mental flexibility and reduced verbal inhibition. She was affected by severe COVID-19 pneumonia, with positive RT-PCR on October 23th.

Due to her crippling neurological disease, she was rejected for tracheal intubation. She was admitted in geriatric intensive care unit, and received full treatment for COVID-19 pneumonia, with corticoids, antibiotics, and high flow oxygen therapy. Despite severe pneumonia and altered general condition, she improved slowly and 15 days after COVID-19 diagnosis, she was able to move her right shoulder when asked, while she was unable to move her right arm for over a year. Right arm rigidity was reduced, and by the end of December 2020, she was able to move her forearm with complete extension and voluntary movements of the hand were possible. She today walks with little help (to prevent backward fall). MRI is unchanged. Brain ¹⁸F-FDG- PET/CT performed on 24th December 2020 showed a mild improvement of the cortical metabolism of glucose in the posterior parietal cortex, and in the occipital and temporal regions, in comparison with the previous tests performed in 2017.

Discussion

We hereby report the first description of unexpected improvement in four patients with chronic neurological disease after recovery from Covid-19 infection. None of them had any conjectural reason for recovery from their chronic condition. We were able to observe and describe these cases because we closely followed up these patients medically with severe disability and living in nursing home. Frequently, patients with long lasting, disabling and hopeless neurologic conditions have no further specialized follow-up.

Improved cognition, behavior and motor function of case 1 was initially reported by his spouse who contacted one of the authors (Dr. Caparros-Lefebvre), to witness an unexpected improvement of neurological condition of this patient, and investigate the likely

causes. This 1st case of neurological improvement was followed by a major amelioration of behavioral disorders in 2 other cases (patient 2 and 3) few weeks later, leading us to hypothesize that this neurological progress could be related to COVID-19 infection.

Up to now, there is no effective treatment of neurodegenerative diseases affecting patient 1 and 4. Both patients have probably predominant tauopathy, even if frontotemporal dementia may be related to different pathological findings, such as DNA binding protein 43 (TDP-43), inclusions of fused-in-sarcoma protein (FUS) or argyrophilic deposits [13]. The brain lesions in all 4 cases are mainly located in the frontal lobe cortex, but as well in basal ganglia, particularly in the putamen and caudate nuclei, in patient with severe anoxia, as well as in patients with neurodegenerative disease [14].

Microglia cells are the primary innate immune cells in the CNS. Since their initial discovery and characterization, several studies have revealed their unique roles not only in maintaining immune homeostasis, but also being indispensable to brain development and cognitive function. Microglia might drive synaptogenesis, neurogenesis and neuronal activity [15]. Microglial cells are highly active in their presumed resting state, continually surveying their microenvironment. Blood-brain barrier disruption provoked immediate and focal activation of microglia [16].

SARS-CoV-2 may reach the cerebral vasculature through the general circulation breaching the blood-brain barrier and invading and injuring the brain parenchyma. SARS-CoV-2 may bind to its receptor Angiotensin Converting Enzyme 2 (ACE2) expressed in endothelial cells of cerebral capillaries, and within the brain parenchyma in both neurons and microglia [17].

We hypothesize that COVID-19 antigens might induce microglial reactivation, leading to an improvement of neurons and cortex metabolism, as observed in case 1. However, microglial cells do have receptors for antibodies; Fc gamma receptors (FcγRs) bind specifically to the Fc (fragment crystallizable) region of IgG immunoglobulin antibodies and are therefore a gateway to responsiveness to various immune stimuli. FcγRs are involved in a variety of microglial biological functions that include phagocytosis, cytokine production, and oxidative bursts [18]. This could make sense with MRI findings in 60 patients, showing a significant increase of gray matter volumes, 3 months after COVID-19 recovery [7]. Therefore, brain ¹⁸F-FDG-PET/CT should be performed in cohorts of patients recovering from COVID-19.

Conclusion

Finally, we encourage all physicians working in rehabilitation units, and/or nursing skills homes, to report any unexplained improvement of chronic neurological diseases after COVID-19 infection, or vaccination. One may hope that COVID-19 vaccination could induce microglial reactivation, as probably did COVID-19 infection.

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