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Covid-19-related encephalopathy: a case series with brain FDG-PET/CT findings

Running title: Covid-19-related encephalopathy

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ABSTRACT

Background A variety of neurological manifestations have been reported in association with Covid-19. Covid-19-related encephalopathy has seldom been reported and studied.

Methods We report four cases of Covid-19-related encephalopathy. The diagnosis was made in patients with confirmed Covid-19 who presented with new-onset cognitive disturbances, central focal neurological signs or seizures. All patients underwent cognitive screening, brain MRI, lumbar puncture, and brain FDG-PET/CT.

Results The four patients were 60 years of age or older, and presented with various degrees of cognitive impairment, with predominant frontal lobe impairment. Two patients presented with cerebellar syndrome, one had myoclonus, one had psychiatric manifestations, and one patient had status epilepticus. The delay between first Covid-19 symptoms and onset of neurological symptoms was between 0 and 12 days. None of the patients had MRI features of encephalitis nor significant CSF abnormalities. SARS-CoV-2 RT-PCR in the CSF was negative for all patients. All patients presented with a consistent brain FDG-PET/CT pattern of abnormalities, namely frontal hypometabolism and cerebellar hypermetabolism. All patients improved after immunotherapy.

Conclusions Despite varied clinical presentations, all patients presented with a consistent FDG-PET pattern which may reflect an immune mechanism.

Keywords: Covid-19, SARS-CoV-2, encephalopathy, encephalitis, FDG-PET/CT

1. INTRODUCTION

Since December 2019, an outbreak of infection caused by the SARS-CoV-2 virus has rapidly spread worldwide. A variety of neurological symptoms have been reported in association with Covid-19, including anosmia and ageusia, cerebrovascular events, and encephalopathy. In a retrospective study of 214 patients, more than a third presented with neurological manifestations. In a report of patients hospitalised in the intensive care unit (ICU), more than a third had dysexecutive symptoms upon discharge, and all brain Magnetic Resonance Imaging (MRI)
showed bilateral fronto-parietal hypoperfusion. While the neuro-invasive potential of SARS-CoV-2, like that of other closely related coronaviruses, is suspected, there are surprisingly few reports of Covid-19 encephalitis. We report four cases of patients with Covid-19-related encephalopathy of suspected immune mechanism, presenting with acute cognitive impairment and brain metabolic abnormalities on 2-desoxy-2-fluoro-D-glucose (FDG) positron emission tomography computed tomography (PET/CT) imaging.

2. MATERIALS AND METHODS

We report consecutive cases of Covid-19-related encephalopathy managed by our multidisciplinary team of infectious diseases physicians, neurologists, and psychiatrists from March 20th to May 16th 2020 in the Pitié-Salpêtrière Hospital in Paris. The diagnosis of Covid-19-related encephalopathy was made in patients with new-onset cognitive disturbances, with central focal neurological signs or seizures in the context of Covid-19, in the absence of another cause of encephalopathy. The diagnosis of Covid-19 was confirmed for all patients by a positive reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay from a nasopharyngeal swab sample. Cognitive performances were assessed using validated screening tests depending on attentional abilities: Mini-mental State Evaluation (MMSE), Frontal Assessment Battery (FAB), praxis abilities. All patients underwent cerebrospinal fluid (CSF) analysis, electroencephalogram (EEG), brain magnetic resonance imaging (MRI), and brain FDG-PET/CT imaging. A comprehensive work-up was done in all patients to rule out alternative
diagnoses of encephalopathy and encephalitis, including herpesvirus PCR in the CSF, antineuronal antibodies in the blood and CSF.

Patients received information and agreed to the use of their medical data in accordance with French regulations. The study received approval from the Sorbonne University Ethic Committee (CER-202028 on 24/04/2020).

3. RESULTS

The main clinical, biological, and imaging features of the patients are summarised in Table 1.

**Patient 1** is a 72-year-old male whose initial Covid-19 symptoms were fever, cough, and anosmia. Fifteen days after Covid-19 onset, he presented with acute psychomotor agitation, cognitive and behavioural frontal lobe syndrome, upper limbs myoclonus, and cerebellar ataxia. CSF examination revealed 6 cells/mm$^3$. Brain FDG-PET imaging on day 23 after Covid-19 onset showed bilateral prefrontal and left-sided parieto-temporal hypometabolism and a slight hypermetabolism within the cerebellar vermis (Figure 1). Covid-19-related encephalitis was suspected. Intravenous polyvalent immunoglobulins (IVIg) 2g/kg were administered and preferred to corticosteroids due to psychomotor agitation. Neurological symptoms improved gradually after IVIg with resolution of myoclonus, cerebellar syndrome, and improvement of frontal signs. Six weeks after Covid-19 onset, cognitive examination was normal.

**Patient 2** is a 66-year-old female who initially presented with fatigue, fever and shortness of breath, and who experienced acute cognitive impairment 7 days after Covid-19 onset. Neurological examination was notable for psychomotor slowing, a cognitive and behavioural frontal lobe syndrome with perseveration, and severe apraxia. Laboratory examinations revealed hypercalcemia (3.2 mmol/L corrected; reference range 2.20-2.55 mmol/L). EEG showed irregular anterior rhythms. Due to persisting cognitive impairment despite correction of hypercalcemia, we administered IVIg from day 14 to day 18 after Covid-19 onset, without notable improvement.
Brain FDG-PET imaging on day 21 showed marked hypometabolism within the bilateral prefrontal and associative posterior cortices and hypermetabolism within the bilateral striatum and the cerebellar vermis (Figure 1). Because of persisting severe cognitive impairment and of the FDG-PET results, we administered intravenous pulse corticosteroids (2mg/kg/day 3 days then 1g/day 3 days). The neurological examination markedly improved in the following days and normalized within two weeks, including cognitive examination (MMSE 28/30, FAB 16/18). Repeat CSF examination showed low beta-amyloid 1-42 (385 pg/ml, normal range 650-2000).

**Patient 3** is a 60-year-old female who complained of acute anxiety, depressed mood, akathisia and gait imbalance on the same day as Covid-19 symptoms (fever, cough and diarrhea) onset. At day 10, neurological examination revealed psychomotor agitation, dysexecutive syndrome, and cerebellar ataxia. Brain FDG-PET at day 14 showed hypometabolism within the bilateral orbito-frontal cortices, and a slight hypermetabolism in the bilateral striatum and cerebellar vermis. Pulse corticosteroids (2mg/kg/day 3 days) were administered. Resolution of the cerebellar syndrome was noted over a few days. Akathisia and anxiety improved within ten days with antidepressant treatment (paroxetine 20mg and mirtazapine 30mg). Six weeks after Covid-19 onset, cognitive examination was normal.

**Patient 4** is a 69-year-old male who was hospitalized in the ICU and intubated due to generalized convulsive status epilepticus 7 days after Covid-19 initial symptoms (fever, fatigue, anosmia and ageusia). EEG showed lateralised periodic discharges in the right frontal lobe, and brain MRI imaging was notable for right orbitofrontal hyperintensities on T2-weighted images. A detailed report of the clinical history, EEG and MRI imaging of patient 4 is under consideration for publication elsewhere. He was treated with antiepileptics (levetiracetam, lacosamide) and IVIg from day 10 to day 14 after Covid-19 onset. After extubation on day 39, neurological examination showed marked psychomotor slowing, frontal cognitive and behavioural syndrome and dyspraxia. Brain FDG-PET on day 41 showed hypometabolism within the bilateral prefrontal and associative posterior cortices, and hypermetabolism within the cerebellar vermis. Pulse corticosteroids (1g/day 5 days) were introduced from day 51 to day 55 with slow improvement ever since. Clinical examination 10 weeks after Covid-19 onset showed improvement of psychomotor slowing, persisting dysexecutive syndrome, improvement of behavioural frontal disturbances and praxis.
Repeat CSF examination revealed high total tau protein (>2000 pg/ml, normal range 150-450) and low beta-amyloid 1-42 (570 pg/ml, normal range 650-2000).

4. DISCUSSION

We report four patients presenting with variable degrees of acute cognitive impairment and focal neurological signs in the context of Covid-19, with a consistent pattern of metabolic abnormalities on brain FDG-PET. Patients were over the age of 60, and had predominant executive and frontal behavioural disorders, sometimes associated with anosmia (Patients 1 and 4), cerebellar syndrome (Patients 1 and 3), myoclonus (Patient 1), or seizures (Patient 4). None of the patients presented with significant CSF abnormalities. SARS-CoV-2 RT-PCR in the CSF was negative for all patients. MRI showed no specific abnormalities. All patients fulfilled diagnosis criteria for possible immune encephalitis according to Graus criteria. 7
Our case series is the first to illustrate FDG-PET findings in patients with Covid-19-related encephalopathy. One case of Covid-19-related anosmia was investigated by brain FDG-PET which showed asymmetrical frontal hypometabolism.\(^8\) Despite varied neurological presentations, our patients presented with a common pattern of hypometabolism in the prefrontal or orbitofrontal cortices and hypermetabolism in the cerebellar vermis. This pattern is distinct from that typically seen in patients with delirium who exhibit global cortical hypometabolism.\(^9\) An association of cortical hypometabolism and striatal, mesiotemporal, and/or cerebellar hypermetabolism has rarely been described in infectious encephalitis, such as in VZV encephalitis.\(^10\) Cerebellar hypermetabolism has seldom been reported in paraneoplastic cerebellar degeneration.\(^11\) The local glucose consumption, and thus 18F-FDG cerebral uptake, correlates with local neuronal and synaptic activity.\(^12\) Neurotransmission and signal transduction are the processes with the highest energetic requirements. Connections between neurons are carried out mainly by excitatory glutamatergic synapses, which account for the great majority of all cortical synapses, yielding an energetic consumption of around 80% of total cortical consumption. A large body of literature demonstrated that 18F-FDG PET adds value to MRI and diagnostic evaluation of several neurological diseases.\(^13,14\) In encephalitis, cortical hypometabolism may be the consequence of varied neuropathological mechanisms: direct blockade of receptors or ion channels by antibodies, direct toxicity/cellular damage due to pathogenic agents or postinfectious healing mechanism. An increased FDG uptake may reflect compensatory mechanisms\(^15\), electro-convulsive phenomena or inflammatory processes (infectious or immune origin) that increase the energy turnover of affected cells.

To our knowledge, there have only been two published cases of Covid-19 with a positive SARS-CoV-2 RT-PCR assay in the CSF,\(^4,6\) and most cases of acute cognitive impairment reported in patients with Covid-19 had no pleocytosis,\(^2\) or only mildly elevated CSF cell counts.\(^5\) In our cases, the new-onset central focal neurological signs or seizures, occurring within the second week after Covid-19 onset in 3/4 patients, the absence of SARS-CoV-2 in the CSF and meningitis, and the FDG-PET findings point towards a parainfectious cytokine storm, post-infectious antibody- or cell-mediated immune mechanism rather than direct viral neuro-invasion. The presence of increased IL-6 in the CSF in 2/2 patients further supports this mechanism. Clinical improvement after immunotherapy is also in keeping with an immune process, although we cannot rule out spontaneous amelioration. Interestingly, similar descriptions of acute cognitive impairment with
diffuse cortical hypometabolism on FDG-PET were reported following therapy with chimeric antigen receptor T-cells, which are known to induce a cytokine storm.\textsuperscript{16}

In the instance of severe Covid-19, cognitive impairment may result from other factors such as hypoxic encephalopathy, metabolic disturbances, side effects of sedation in the case of ICU patients. The diagnosis of Covid-19 related encephalitis or encephalopathy may be further confounded by acute delirium revealing underlying cognitive deficits, or epilepsy. Notably, patient 2’s cognitive disturbances could be partly induced by hypercalcemia, and patient 4’s initial psychomotor slowing could have been secondary to prolonged sedation and/or post-ictal confusion. Importantly, patient 2 and patient 4 both presented with anterior EEG abnormalities, consistent with what has been previously shown in Covid-19 patients with encephalopathy.\textsuperscript{17} It is noteworthy that these two patients had abnormal neurodegenerative markers in the CSF, namely isolated low beta-amyloid for patient 2 and high tau with low beta amyloid for patient 4. It is possible that an underlying neurodegenerative disease may have been a predisposing factor for neurological manifestations in the context of Covid-19. Elevated tau protein in patient 4 could also reflect neuronal damage due to encephalitis and/or status epilepticus.

Brain FDG-PET imaging should be considered in patients with Covid-19 presenting with acute central nervous system impairment. Further studies with longitudinal FDG-PET imaging will be important to determine the pathophysiological bases of the pattern of cortical hypometabolism and cerebellar hypermetabolism, and whether these abnormalities are due to functional inactivation rather than irreversible brain damage.
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DECLARATIONS OF INTEREST
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DATA AVAILABILITY
Detailed data is available upon request to the corresponding author.

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FIGURE LEGEND

Figure 1 (color Figure): Brain FDG-PET/CT imaging in 4 patients with Covid-19 and acute cognitive impairment.
Table 1: Clinical and laboratory features of 4 patients with Covid-19 and acute cognitive impairment.

|                     | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|---------------------|-----------|-----------|-----------|-----------|
| **Age (years)**     | 72        | 66        | 60        | 69        |
| **Sex**             | M         | F         | F         | M         |
| **Past medical history / Comorbidities** | None | None | Temporal lobe epilepsy (hippocampal sclerosis) | Diabetes mellitus type 2, hypertension |
| **Clinical features at admission** | | | | |
| **Covid-19 symptoms** | Fever, cough, anosmia | Fever, fatigue, shortness of breath | Fever, cough, diarrhea | Fever, fatigue, anosmia, ageusia |
| **Supplemental oxygen** | Yes | Yes | No | Yes |
| **Mechanical ventilation** | No | No | No | Yes |
| **Delay between Covid-19 onset and neurological symptoms (days)** | 12 | 7 | 0 | 7 |
| **Neurological symptoms** | Psychomotor agitation, frontal lobe syndrome (MMSE 25/28, FAB 13/18), cerebellar syndrome (static), myoclonus | Psychomotor slowing, frontal lobe syndrome, apraxia (MMSE 9/30, FAB 2/18) | Psychomotor agitation, anxiety, depressed mood, dysexecutive syndrome (FAB 11/18) cerebellar syndrome (hypotonia, gait ataxia, dysmetria, dysarthria, nystagmus) | Generalized convulsive status epilepticus, frontal lobe syndrome (FAB 3/18) |
| **Cerebrospinal fluid testing** | | | | |
| **Cellularity, cells/mm³ (reference < 5)** | 6 | 1 | 0 | 1 |
| **Protein levels, g/L (reference 0.15-0.45)** | 0.23 | 0.3 | 0.25 | 0.66 |
| **Oligoclonal bands** | Absent | Absent | Absent | Absent |
| **IL-6 levels in CSF,** | 13 | NP | NP | NP |
| Abbreviations : CSF, cerebrospinal fluid; EEG, electroencephalogram; FAB, Frontal Assessment Battery; FDG-PET/CT, 2-desoxy-2-fluoro-D-glucose positron emission tomography computed tomography; IL-6, interleukin 6; MMSE, Mini-mental State Evaluation; MRI, magnetic resonance imaging; NP, not performed; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus |
