


CASE REPORT

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Creutzfeldt–Jakob disease in a post-COVID-19 patient: did SARS-CoV-2 accelerate the neurodegeneration?

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Abstract

Background Creutzfeldt–Jakob disease (CJD) is a rare, fatal neurodegenerative disorder, with few months as a usual duration from onset to death.

Case presentation In this case report, a patient of Sporadic CJD (sCJD) who presented one month after severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. The diagnosis of this case was established after confirming findings from clinical, neurophysiology, radiological, and laboratory features of this disease.

Conclusion Putting in mind all the updated data on the pathogenesis of CJD and the immune responses to SARS-CoV-2, we can suggest that COVID-19 can lead to accelerated pathogenesis and exaggerated manifestations of this fatal neurodegenerative disease.

Keywords Sporadic Creutzfeldt–Jakob disease (sCJD), SARS-CoV-2, COVID-19, PET/MRI brain, Neurodegenerative disorder

Background

Creutzfeldt–Jakob disease (CJD) is a rare degenerative cause of rapidly progressive neurological dysfunction, affecting about one in every 1 million persons every year worldwide [1]. There are four described types of CJD; sporadic, familial, iatrogenic, and variant. Sporadic CJD (sCJD) is the most common form and accounting for 85% of CJD cases [2]. Early diagnosis, despite the heterogeneity of symptoms in early stages of the disease, is critical

for the patient and their family members, to achieve optimal management and to dodge the chances of iatrogenic transmission [3, 4].

The pathophysiology behind CJD is the accumulation of abnormal PrP^{Sc} proteins in the central nervous system [5]. Usually, CJD appears in 55–75-year-old patients, with mortality of about 90% of cases over 1 year of the illness [6]. Myoclonus is the hallmark feature of CJD, yet it can present with behavioral changes, amnesia, and gait instability. In accordance with recent clinical diagnostic criteria for CJD, parietal, occipital, and temporal cortical regions are the most affected areas in MRI imaging. Hyperintensities in at least two of these areas are pathognomonic as well as sharp-wave complexes on the electroencephalography (EEG) or detection of 14-3-3 protein in the cerebrospinal fluid (CSF) [7].

On the other hand, the neurological effect of SARS-CoV-2 is not well-explained. Neurological manifestations of SARS-CoV-2 may include anosmia, headache,

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ischemic stroke, delirium, and encephalitis [8]. Besides the current evidence that SARS-CoV-2 can infect the nervous system directly, there are also suggested mechanisms for indirectly mediated inflammatory affection the nervous system [9, 10]. Moreover, the storming release of pro-inflammatory cytokines as IL-1, IL-6, IL12, and TNF α is suggested to cause neuroinflammation and can accelerate neurodegeneration process [11–16].

Here, the reported case demonstrates the clinical, radiological and laboratory features of sCJD in a post COVID-19 patient, with very rapid deterioration. This draws attention to some of the challenges faced during diagnosing patients with such rare neurodegenerative disease, and how these have been exaggerated by COVID-19.

Case presentation

A 73-year-old previously healthy man was complaining of fever, cough and loss of smell on the 18th of March 2021. The lung CT scan, lymphopenia, and the positive result of SARS-CoV-2 PCR test confirmed the diagnosis of COVID-19. For which he received the recommended home therapeutic protocol with marked improvement.

One month later, he started to complain of inattention, recent memory impairment, depressed mood, urinary

incontinence and gait instability. Routine blood tests were normal, and a second SARS-CoV-2 PCR test was negative. Brain MRI showed mild periventricular leukoencephalopathy, bilateral fronto-parietal small infarcts at different stages of evolution, with central and, to a lesser extent, cortical cerebral involutinal changes that raised the possible diagnosis of normal pressure communicating hydrocephalus (Fig. 1). However, CSF flowmetry study was done and showed no radiological evidence of hyperdynamic flow across the aqueduct. In addition, CSF analysis was acellular, with normal opening pressure, normal proteins and glucose levels with no bacterial growth in culture, negative HSV-PCR, tumor markers and serum autoimmune encephalopathy panels. EEG showed abnormal bilateral symmetrical and synchronous moderately diffuse cerebral slowing of 4–5 Hz; mixed delta–theta activity (Fig. 2).

The patient's condition deteriorated rapidly, as he became confused, disorientated to place with excessive daytime sleepiness, restless sleep, and loud snoring with periods of silence followed by gasps. Polysomnography was done and showed sleep efficiency of 74.5%, reduced REM and absent slow-wave sleep with apnea–hypopnea index of 36.3 events/hour, average awake SpO₂ was 94% with lowest SpO₂ 80% during periods of apnea during

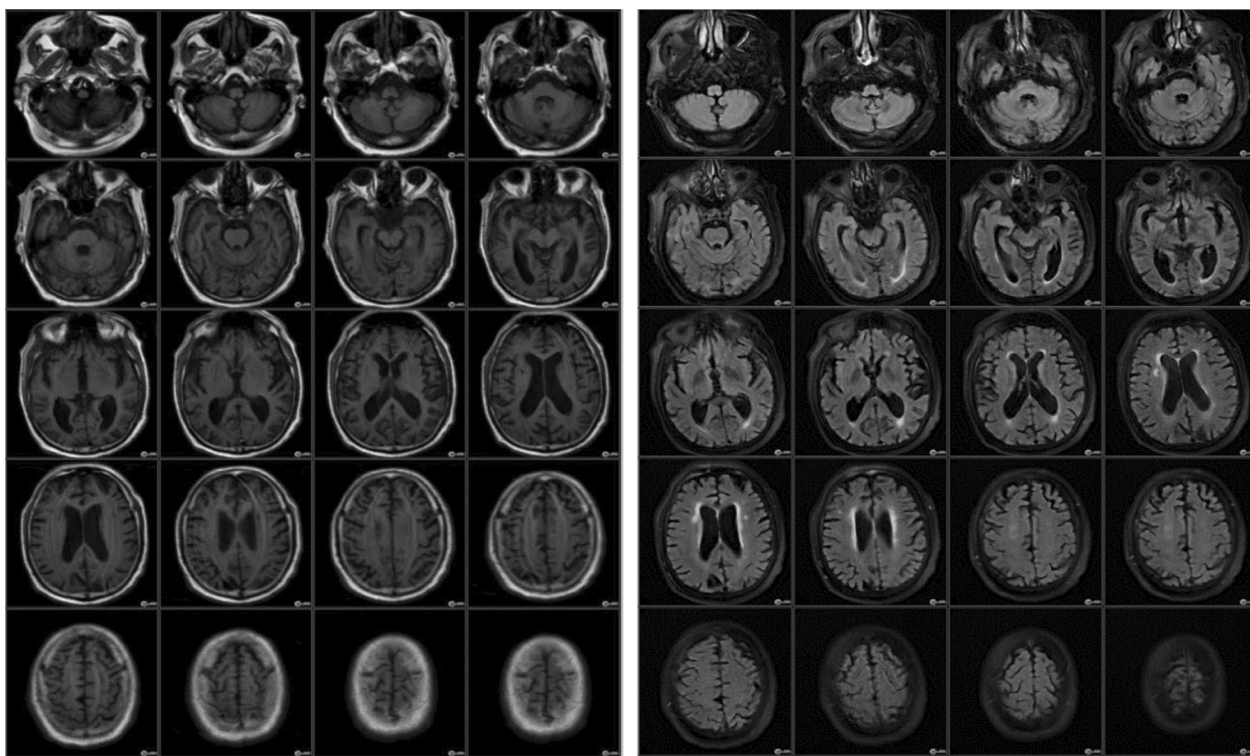


Fig. 1 MRI brain axial T1 and FLAIR showing mild periventricular leukoencephalopathy, bilateral fronto-parietal small infarcts and central and to less extant cortical cerebral involutinal changes

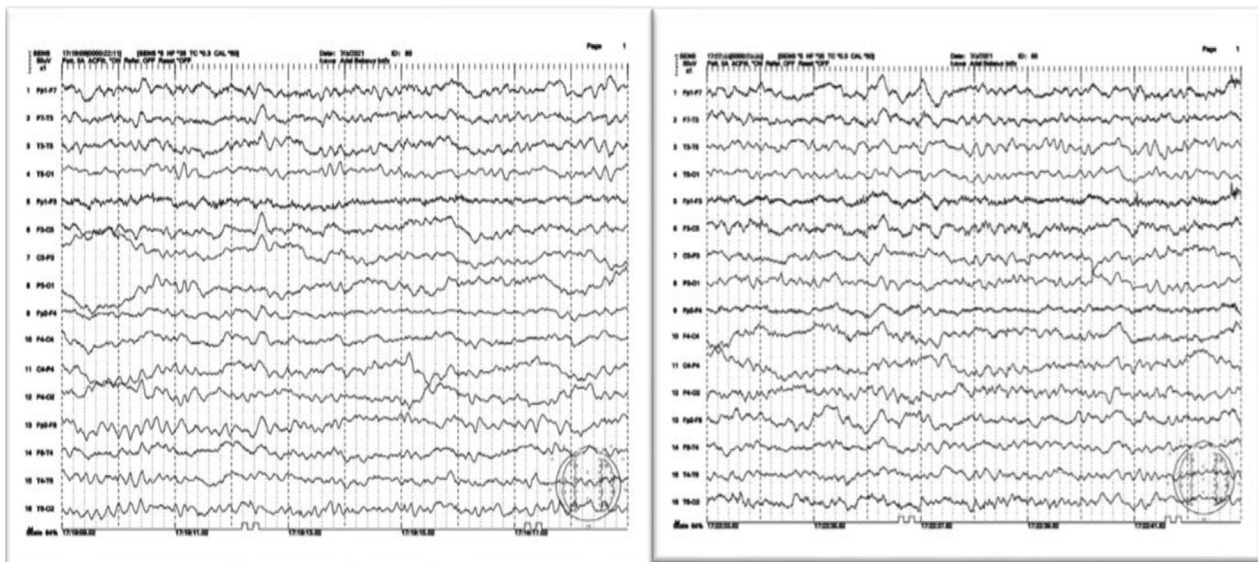


Fig. 2 Abnormal EEG record showing moderate diffuse cerebral slowing

sleep. A diagnosis of severe obstructive sleep apnea was suggested that might be attributed to COVID-19 illness (Fig. 3), yet BiPaP ventilation trail showed no significant improvement. The patient's condition deteriorated progressively, as he failed to recognize his family members, with anomia, poor comprehension, executive

dysfunction, and recurrent attacks of intermittent diffuse myoclonic jerks.

Multi-parametric ^{18}F -FDG hybrid PET/MRI brain scan revealed abnormal relative diffusion restriction at the deep gray matter nuclei, particularly the caudate nuclei and the anterior aspects of the putamen

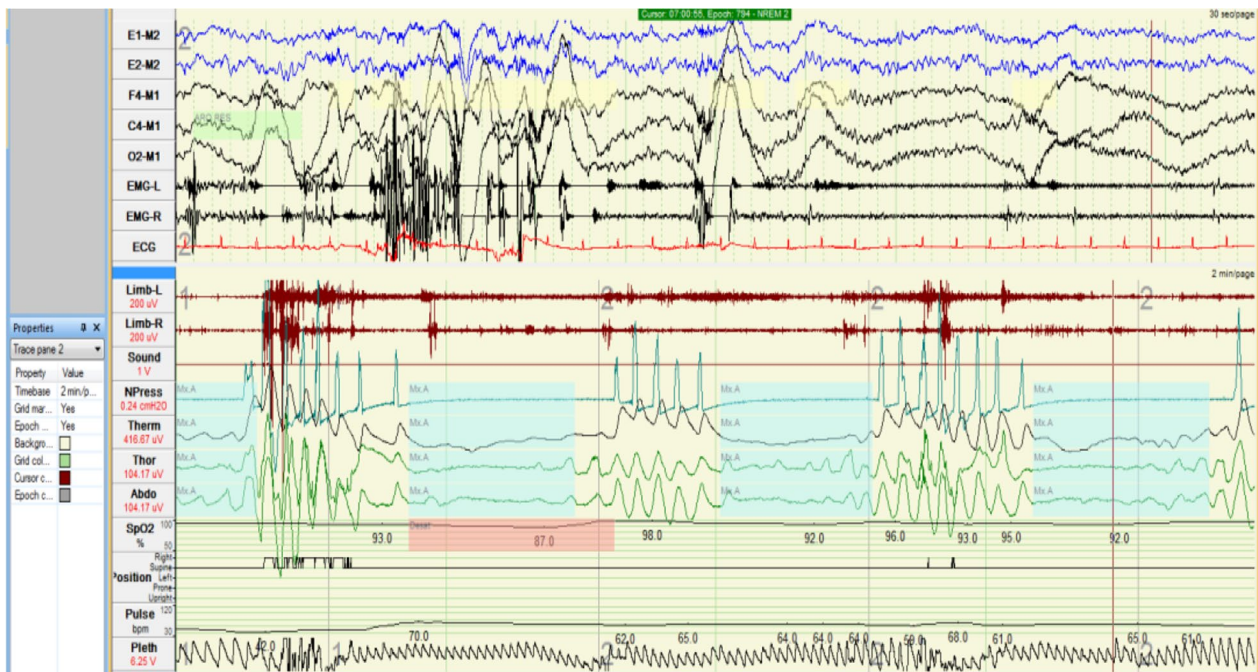


Fig. 3 Polysomnography showing severe degree of obstructive sleep apnea

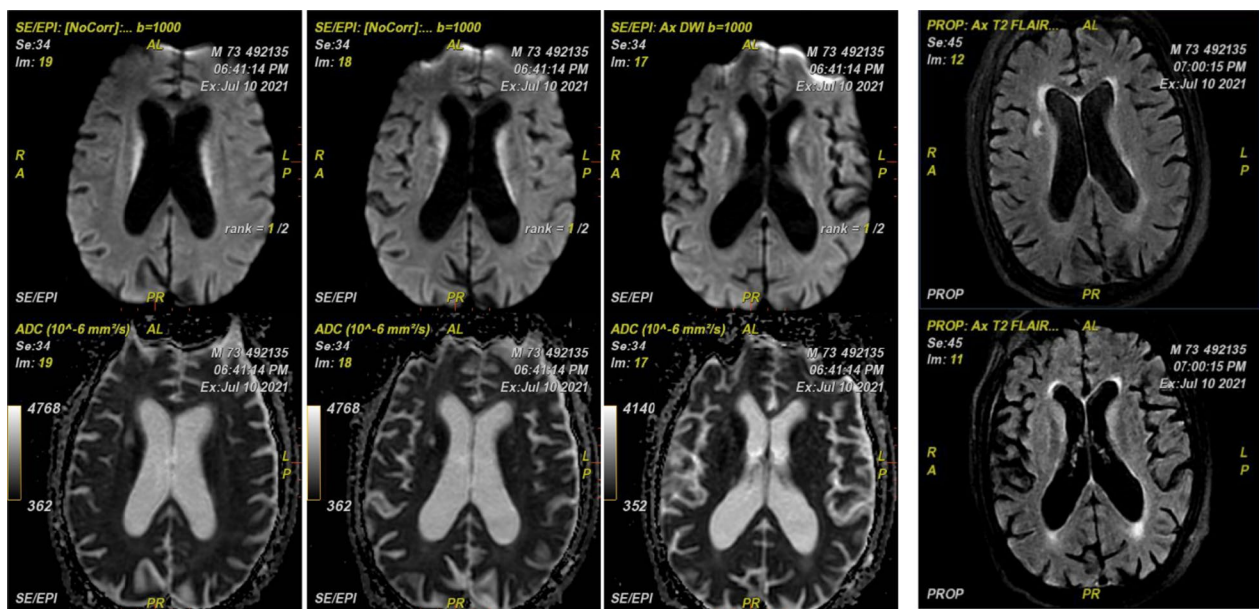


Fig. 4 Conventional MRI data with diffusion images showing abnormal relative diffusion restriction with faint abnormal high signal on FLAIR, at the deep gray matter nuclei particularly caudate nuclei and anterior aspects of the putamen and thalamic nuclei

and thalamic nuclei (Fig. 4). These findings are mostly suggestive of CJD, particularly the sporadic form, and also ruled out COVID-19-related encephalopathy, as the later would have pronounced white matter affection deeply and to a lesser extent superficially. Moreover, MR perfusion data showed mild hypoperfusion status of the deep cerebral white matter and deep gray matter bilaterally. The hippocampal formations and the precuneus regions are of normal perfusion for this age, which can more or less rule out Alzheimer's disease diagnosis (Fig. 5). PET/MR data showed an evident hypometabolic status seen regarding the cortical regions

particularly at the bilateral lateral prefrontal and to a lesser extent bilateral medial prefrontal regions. The precuneus, posterior cingulum, occipital lobes and temporal lobes were spared from such hypometabolism ruling out other causes of dementia like Lewy body dementia (Figs. 6, 7).

CSF 14-3-3 protein assay was ordered revealing a positive result. During hospitalization, the patient was treated with high doses of corticosteroids before the diagnosis of sCJD was suggested, but there was no significant improvement. Unfortunately, his neurologic status

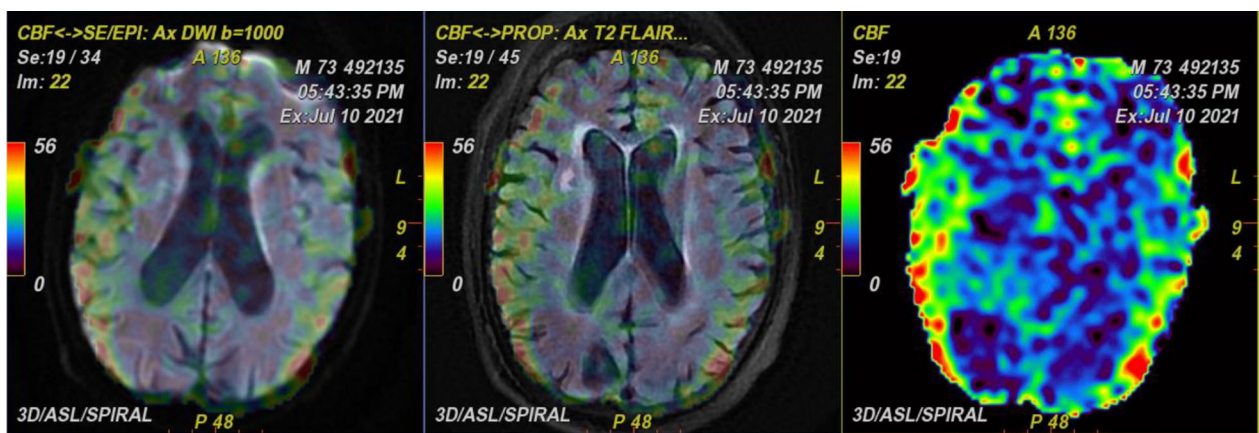


Fig. 5 MR perfusion images showing mild hypoperfusion status of the deep cerebral white matter and deep gray matter bilaterally but with of normal perfusion of hippocampal formations and the precuneus regions

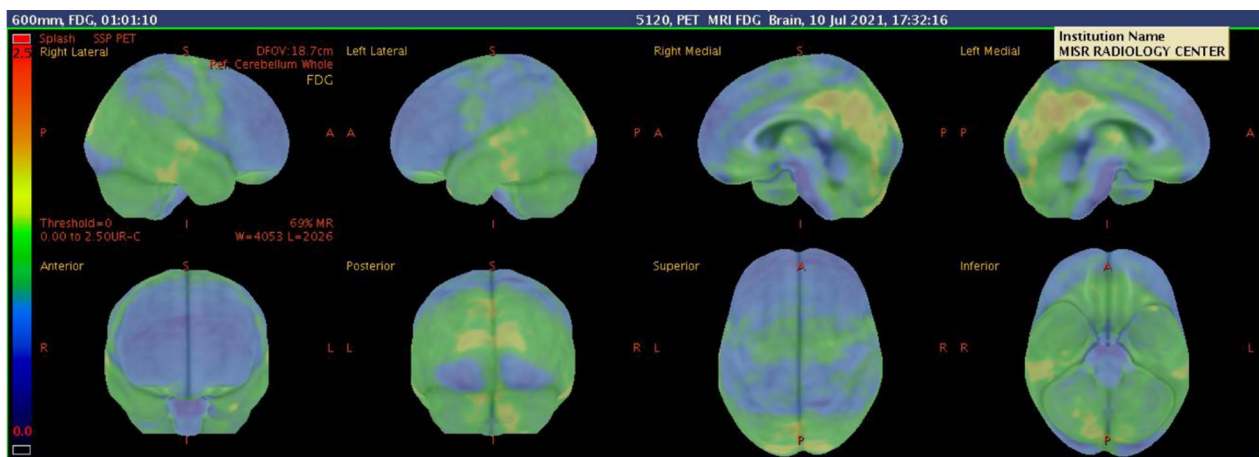


Fig. 6 PET/MR data showing hypometabolic status seen regarding the cortical regions particularly at the right and left lateral prefrontal with sparing of the precuneus and posterior cingulum and occipital lobes and temporal lobes

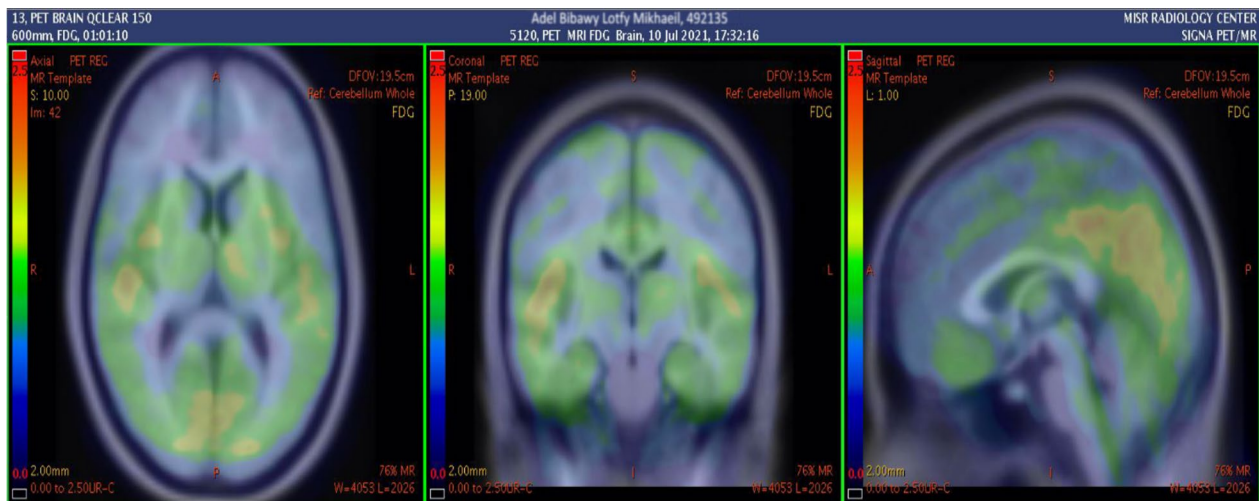


Fig. 7 PET/MR data showing hypometabolic status of right and left medial prefrontal regions

progressed to mutism, vegetative state, and coma. Sadly, he died three months after the symptoms' onset.

Since the development of COVID-19 pandemic, there have been many reports of neurological insults directly related to the SARS-CoV-2 infections. While cerebrovascular strokes seem to be the most frequent neurological sequelae, encephalopathies, encephalitis and neuropsychiatric disorders have been also reported [8, 17]. COVID-19 was our first suggested diagnosis for our patient; however, this suggestion was excluded following the negative result of his SARS-CoV-2 PCR test, supported with the absence of specific brain MRI findings observed in patients with COVID-19 as diffuse leukoencephalopathy, restricted diffusion and juxtacortical and callosal microhemorrhages [18].

The sCJD is usually fatal within months, yet about 15% of sCJD patients survive for more than two years [6]. In our case presented here, the rapid deterioration, as the patient died just four months after the onset of the disease, raises the suspicion of the presence of additional precipitating factor. Generally in prion disease, reactive A1 astrocytes are believed to have a neurotoxic effect and act as foci for PrP^{Sc} propagation [19]. The concurrence of CJD in this post-COVID-19 patient has directed us to a hypothesis that the systemic inflammatory mediators storm occurring with COVID-19 may have accelerated the CJD pathogenesis and hence the rapid progression of neurodegeneration. There is an observational support for this hypothesis,

as the inflammatory storm occurring in COVID-19 releases massive amounts of inflammatory mediators that are enough for activation A1 astrocytes which is directly related to PrP^{Sc} propagation as stated earlier [20–22].

Two case reports recently concluded that there is a sudden surge in the systemic inflammatory response due to COVID-19 and concluded the same hypothesis of accelerated progression of sCJD cases [23–25].

Conclusions

When a patient of sCJD gets infected with SARS-CoV-2, the neurological deterioration gets accelerated, exacerbated, and consequently shortening the overall survival period. Therefore, extra-vigilance and intensive monitoring for such patients is highly recommended.

Abbreviations

BiPaP	Biphasic positive airway pressure
CJD	Creutzfeldt–Jakob disease
COVID-19	Coronavirus disease 2019
CSF	Cerebrospinal fluid
EEG	Electroencephalography
HSV	Herpes simplex virus
IL	Interleukins
PCR	Polymerase chain reaction
PrP ^{Sc}	Scrapie isoform of the prion protein
SARS-Cov-2	Severe acute respiratory syndrome coronavirus-2
sCJD	Sporadic Creutzfeldt–Jakob disease
TNF	Tumor necrosis factor

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Author contributions

TA, AA: design and conceptualized manuscript, collecting the data, drafted the manuscript for intellectual content. YA, AZ: data collection, drafting and revision of manuscript. KO, HS: designing, drafting and revision of manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

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Availability of data and materials

The data sets generated and analyzed during the current study are not publicly available due to institutional limitations, yet they are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the ethical committee of Faculty of Medicine, Ain Shams University in May 2021.

Consent for publication

Patient provided informed written consent for publishing case-related data.

Competing interests

The authors declare that they have no competing interests.

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