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Creutzfeldt-Jakob disease in a man with COVID-19: SARS-CoV-2-accelerated neurodegeneration?

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ABSTRACT

We describe a man whose first manifestations of Creutzfeldt-Jakob disease occurred in tandem with symptomatic onset of coronavirus disease 2019 (COVID-19). Drawing from recent data on prion disease pathogenesis and immune responses to SARS-CoV-2, we hypothesize that the cascade of systemic inflammatory mediators in response to the virus accelerated the pathogenesis of our patient's prion disease. This hypothesis introduces the potential relationship between immune responses to the novel coronavirus and the hastening of preclinical or manifest neurodegenerative disorders. The global prevalence of both COVID-19 and neurodegenerative disorders adds urgency to the study of this potential relationship.

A previously healthy man in his 60s developed fever several days after co-habitant family members were diagnosed with COVID-19. He became confused, slowed and forgetful, and tested PCR positive for SARS-CoV-2. Over two weeks his disorientation worsened, he developed paucity of speech with paraphasic errors, and unsteady gait with intermittent right-hand clenching. On admission he was inattentive and perseverative, with non-fluent discourse, anomia, impaired comprehension, phonemic paraphasias, and intermittent myoclonic jerks of the right arm. Laboratory studies revealed abnormal inflammatory markers (summarized in Table 1). Cerebrospinal fluid (CSF) was acellular, with normal opening pressure, protein, glucose, bacterial culture, IgG and banding pattern, and HSV PCR. CSF and serum autoimmune encephalopathy panels were negative. Electroencephalogram (EEG) revealed abundant 1–1.5 Hz left lateralized periodic discharges and diffuse delta-theta slowing (Fig. 1). Brain MRI revealed restricted diffusion (Fig. 2, A-D) with corresponding FLAIR hyperintensity throughout left hemisphere cortex, and in left caudate nucleus and thalamus. Brain 18-F fluorodeoxyglucose (FDG) positron emission tomography (PET) revealed hypometabolism in areas of MRI abnormalities (Fig. 2, E-F), with crossed right cerebellar diaschisis. He was treated with IVIG and methylprednisolone until CSF RT-QuIC, 14-3-3 and T-tau resulted 2 weeks later confirming the suspicion for Creutzfeldt-Jakob disease (CJD). Neurologic status progressed to mutism, right hemiplegia, spontaneous multifocal myoclonus, somnolence and agitation. He died 2 months after symptom onset.

1. Discussion

Neurological manifestations of COVID-19 include headache, delirium, anosmia, increased stroke risk, dizziness, and encephalitis (Wu et al., 2020). This first report of CJD in a patient with COVID-19 may reflect pure coincidence, given the high, likely underestimated, prevalence of clinically manifest and asymptomatic COVID-19, and the annual incidence of CJD of approximately 1 per million. However, this case raises the specter of a clinically meaningful interaction in which infection with SARS-CoV-2 precipitates or accelerates neurodegenerative diseases.

Animal and human studies of neurodegenerative disease and brain injury show that release of pro-inflammatory cytokines – IL-1, IL-6, IL-12, and TNFα by activated microglia or reactive A1-astrocytes in the course of a systemic immune response promote neuroinflammation and may accelerate disease progression in Alzheimer disease (Holmes et al., 2009), Parkinson disease (Tan et al., 2020), multiple system atrophy (Hoffmann et al., 2019), frontotemporal dementia (Bright et al., 2019), progressive supranuclear palsy, primary progressive aphasia, and stroke (Khandelwal and Herman, 2011). Fast neurodegeneration is associated with elevation of plasma IL-13, TNF- α and G-CSF in rapidly progressive AD (Stoeck et al., 2014).

CJD is caused by the accumulation of abnormally folded, protease-resistant isoforms of host cellular sialoglycoproteins (i.e., prion proteins). Accumulation predominantly of prion protein scrapie, PrPSc, leads to vacuolation and spongiform neuropathologic changes coinciding with rapid neurodegeneration and activation of astrocytes and

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Table 1
Abnormal inflammatory markers and reference ranges.

Laboratory results:	Reference range (units)
D-dimer 964	<500 (ng/ml)
Ferritin 1002	20–300 (μg/L)
C-Reactive Protein 2.9	<8.0 (mg/L)
Erythrocyte Sedimentation Rate 80	0–13 (mm/hour)
Creatine Kinase 49	60–400 (U/L)
High Sensitivity Troponin T 15	0–14 (ng/L)
Fibrinogen 565	150–400 (mg/dL)
Lymphocytes 0.79	1.0–4.8 (K/μL)

microglia in affected regions. Animal studies demonstrate accelerated transition from pre-clinical to clinical stages of prion disease in settings of co-infection. Mice co-infected with *T. muris* after direct CNS PrPSc injections developed a polarized immune response with increased CD8+ T cell recruitment, and elevated levels of pro-inflammatory cytokines including IFN-γ, and enhanced activation of A1 reactive astrocytes that significantly shortened time to development of clinical signs (Donaldson et al., 2020).

Depending on local milieu, astrocytes may be induced to assume one of two distinct reactive forms: a neurotoxic A1 phenotype and a neuroprotective A2 phenotype. A1 astrocytes potentiate death of neighboring neurons and oligodendrogliocytes (Liddelow et al., 2017). Il-1, TNF and C1q are collectively necessary and sufficient for A1

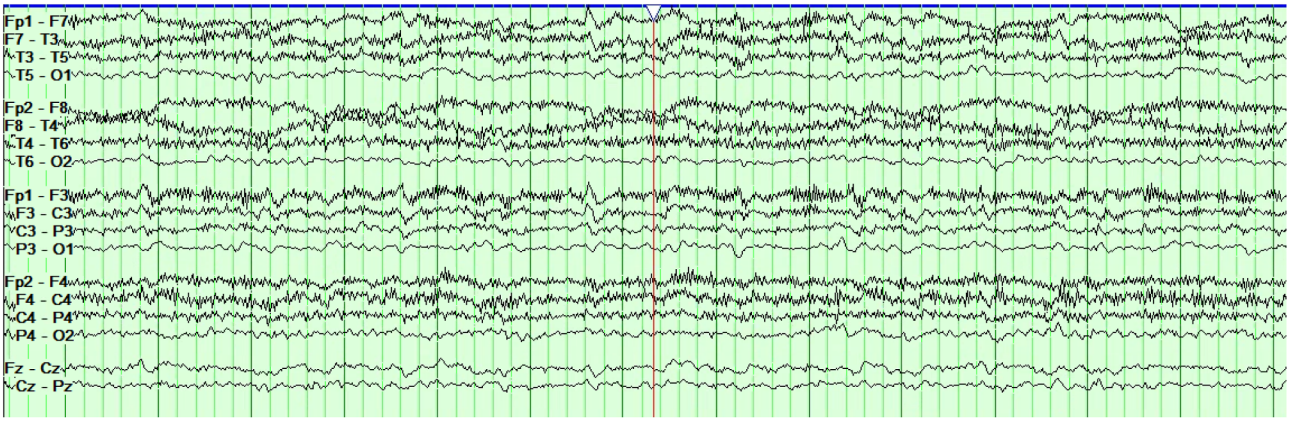

Fig. 1. EEG recording demonstrates frequent 1 Hz left-sided lateralized periodic discharges, with diffuse delta-theta slowing of the background more prominently on the left.

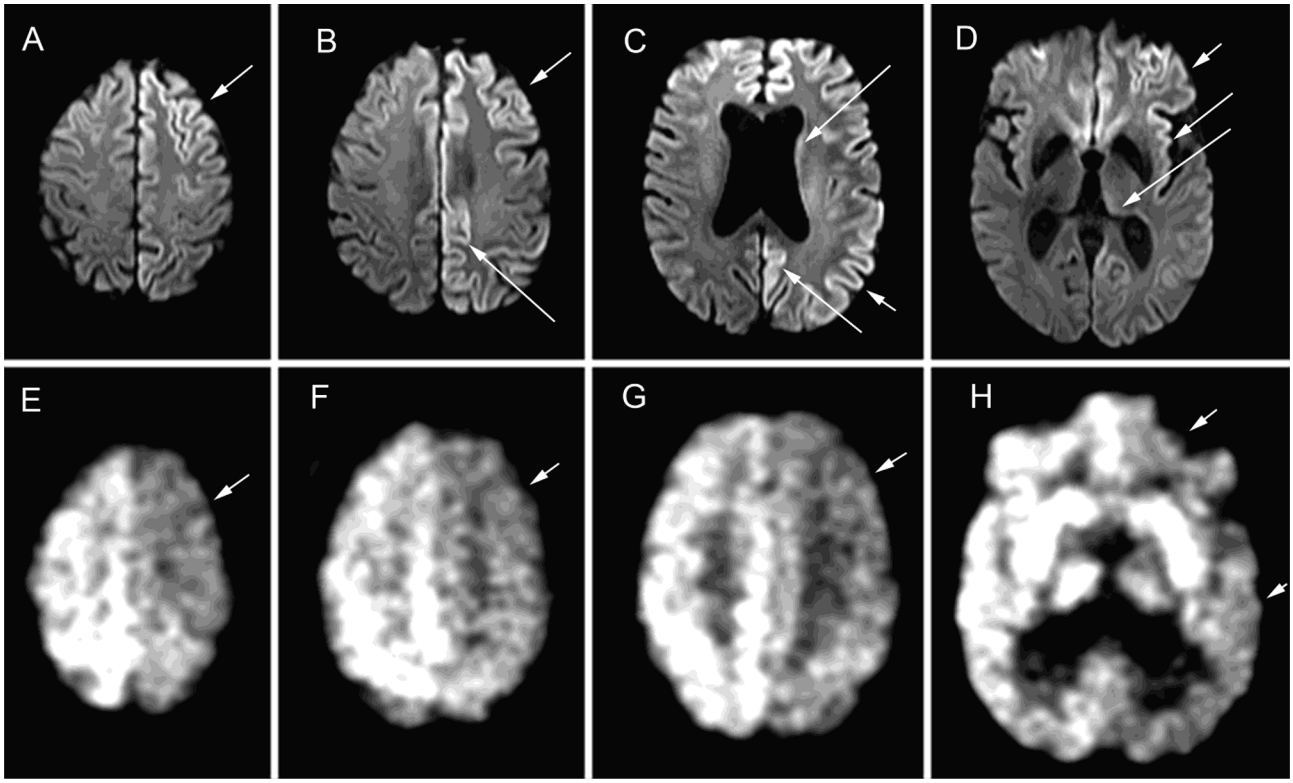

Fig. 2. A – D: Brain MRI findings in this case. Diffusion weighted images from A, superior to D, inferior brain regions showing asymmetric restricted diffusion (bright signal, arrows) in the cortical ribbon more prominently in the left hemisphere in prefrontal, posterior parietal and retrosplenial cortices, as well as the insula and cingulate gyrus, with faint signal abnormality also in the body of the caudate nucleus (in C) and pulvinar of thalamus (in D). E-F: 18-FDG PET findings in this case, showing hypometabolism in areas of restricted diffusion.

astrocyte activation (Liddelow et al., 2017). In prion disease, A1 reactive astrocytes are thought to be neurotoxic by mediating neuronal damage of adjacent neuronal processes and serving as foci for PrPSc propagation (Makarava et al., 2020). Pre-clinical CJD is marked by retention of region-specific homeostatic identities of glia, including astrocytes. During the transition to clinical CJD these region-specific signatures are lost and replaced by a neuroinflammatory transcriptome signature that affects astrocyte sub-populations in a region-dependent manner (Makarava et al., 2020).

The simultaneous clinical presentations of COVID-19 and CJD in this patient led us to hypothesize that the cascade of systemic inflammatory mediators that characterize COVID-19 may have accelerated the prion disease pathogenesis and neurodegeneration by facilitating loss of region-specific homeostatic identities of astrocytes and fostering a neuroinflammatory transcriptional signature. The molecular mechanism remains to be determined, but there is empirical support for our hypothesis in that there is inflammasome activation and increased secretion of Il-1 (Cavalli et al., 2020), TNF and complement cascade in COVID-19 (Merad and Martin, 2020), and the fact that Il-1, TNF and C1q are necessary and sufficient for activation of A1 astrocytes (Liddelow et al., 2017) which affect prion propagation.

Lateralized presentation of CJD has been reported previously. Notably, lateralized modulation of immune function (Neveu, 2002) and inter-hemispheric asymmetry in basal levels of cytokines and distribution of microglia are documented (Fu et al., 2003), perhaps predisposing to asymmetric prion disease propagation and neurodegeneration, and compounded by systemic inflammatory responses.

Neurological dysfunction in COVID-19 is likely caused by immune responses systemically and within the nervous system (Farhadian et al., 2020). Our hypothesis that inflammatory responses to SARS-Cov-2 precipitate or exacerbate neurodegenerative disease is urgent because COVID-19 portends disproportionately worse outcomes in the elderly who are already at risk of neurodegenerative disease.

Ethics statement

Consent was obtained for publication by the relatives/health care agent, and all identifiable information removed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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