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LETTER TO THE EDITOR

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The diagnosis of Creutzfeldt–Jakob disease in a SARS-CoV-2-infected patient should be confirmed by brain biopsy or autopsy

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Abstract

This letter to the Editor discusses the case of a 73-year-old male with mild SARS-CoV-2 infection who one month later developed rapidly progressive cognitive decline, and imaging findings suggestive of Creutzfeldt–Jakob disease (CJD). The diagnosis of sporadic CJD was made on the basis of clinical presentation (rapidly progressive decline, depression, gait disturbance, incontinence, mutism), cerebral MRI (small infarcts, atrophy), hybrid FDG-PET (putaminal and thalamic diffusion restriction, bifrontal hypometabolism), and elevated 14-3-3 in the cerebrospinal fluid (CSF). Despite administration of glucocorticoids, the patient died three months after the onset of symptoms. No autopsy was performed. This case raises the question of a possible link between SARS-CoV-2 infection and the subsequent development of CJD-like syndromes, which warrants further investigation.

Keywords Creutzfeldt–Jakob disease, SARS-CoV-2 infection, EEG, Neurodegenerative disease, Immune competence

Introduction

To the Editor

We read with interest the article by Alloush et al. about a 73-year-old male diagnosed with Creutzfeld–Jacob disease (CJD), which began clinically manifesting four weeks after a mild SARS-CoV-2 infection [1]. CJD was diagnosed based on clinical presentation, imaging, and exclusion of various differential diagnoses [1]. The patient died three months after onset [1]. No autopsy was performed. The study is impressive, but some points require discussion.

Main text

The first point is that several arguments speak against a causal relationship between SARS-CoV-2 and CJD. First, there is no evidence that the prevalence of CJD has increased during the pandemic, as confirmed by an Australian study [2]. There is also evidence from other countries, such as the UK, that the prevalence of CJD has not increased during the pandemic (148 CJD cases during the pandemic and 141 CJD cases in the comparator) suggesting a global trend [3]. Second, there are only few cases of CJD patients who suffered from SARS-CoV-2 infection or cases with SC2I who later developed CJD [4, 5]. Third, there is no evidence that SARS-CoV-2 vaccination has reduced the prevalence of CJD. Fourth, the incubation period of CJD is long. Although the exact incubation period is not known, it is estimated to be 11–15 years [6, 7]. This is because the prevalence of patients with variant CJD exposed to bovine spongiform encephalopathy (BSE) in the 1980s, peaked in 2000 [6].

The second point is the diagnosis of CJD. According to the most recent diagnostic criteria published by the Centers for Disease Control and Prevention in 2018, a firm diagnosis of CJD can only be made by a positive brain tissue test [8]. This includes standard neuropathological techniques (i.e., histology and immunohistochemistry)

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and/or Western blot confirmed protease-resistant prion protein [8]. This test can be performed at either a brain biopsy or an autopsy [8]. Neither procedures were performed in the index case, which may be due to the practical difficulties of performing a biopsy or autopsy and the risk of infection associated with prion diseases. Therefore, at best, the patient can be diagnosed with probable CJD. Diagnostic criteria for probably CJD include a positive real-time quaking-induced conversion in CSF or dementia accompanied by at least two of myoclonus, visual, or cerebellar impairment, pyramidal or extrapyramidal signs, or akinetic mutism and at least one positive criterion of electroencephalography suggestive of CJD, positive CSF 14–3-3, high signal in the caudate/putamen, or at least two cortical regions (temporal, parietal, occipital) on either diffusion-weighted imaging or fluid-attenuated inversion recovery [8].

A third point is that the CSF has not been tested for viruses other than HSV, including SARS-CoV-2. In addition, cerebral magnetic resonance imaging with contrast has not been reported to rule out infectious or immune encephalitis. In addition, antibodies associated with autoimmune encephalitis (AIE) were only determined in the serum, but not CSF, and it was not mentioned which specific AIE-associated antibodies were examined. Before attributing the clinical presentation to CJD, it would have been imperative to rule out all possible causes of infectious and autoimmune encephalitis. The CSF cell count may be normal in encephalitis, especially early in the disease [9]. In a retrospective study of 597 patients with all-cause encephalitis, only 446 (75%) had pleocytosis, while 25% did not [9]. Among patients with infectious encephalitis, 19% had no pleocytosis [9]. Other possible causes of rapid cognitive decline that should have been considered include neurosyphilis, vascular dementia, frontotemporal dementia, DPPX-associated encephalitis, Borna virus-associated encephalitis, ITPR1-associated encephalitis, Lewy-body dementia, septic encephalitis, lymphocytic leukemia, Hashimoto encephalopathy, vitamin-B12 deficiency, Whipple's disease, typhus encephalopathy, HIV, progressive multifocal leukoencephalopathy (PML), and subacute sclerosing panencephalitis [10].

Surprisingly, lumbar puncture was not repeated to correlate the clinical course with the results of CSF studies. Analysis of cytokines, chemokines, glial factors, tau, neurofilament, serpin pathway proteins, complement factors, glycoprotein-alpha-2, glycoprotein-alpha-1, linear RNAs, and circRNAs in the CSF, which can be elevated in SC2I with central nervous system involvement, is also lacking.

Future studies should focus on the pathophysiological relationship between CJD and SC2I, in particular on how many of the individuals with long-COVID may develop CJD in the future. In addition, a possible causal relationship between SARS-CoV-2 infection and CJD needs to be investigated in appropriate animal and cell models.

Conclusions

The diagnosis of definite CJD should be confirmed by a brain biopsy or autopsy, despite the logistic and financial challenges. In addition, all alternative causes of rapid cognitive decline must be ruled out before diagnosing CJD. This includes not only common causes of infectious and immune encephalitis but also rare causes of neurodegenerative, genetic, and metabolic cerebral disease. A causal link between SARS-CoV-2 and CJD is unlikely, as the prevalence of CJD did not increase during the pandemic, only a few cases with SARS-CoV-2 infection that developed CJD were reported, the SARS-CoV-2 vaccination had no impact on the prevalence of CJD, and the suspected incubation period of CJD is between 11 and 15 years.

Abbreviations

BSE	Bovine spongiform encephalopathy
CJD	Creutzfeldt–Jakob disease
CSF	Cerebrospinal fluid
DWI	Diffusion-weighted imaging

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Competing interests

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