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Confronting the Unexpected: A Case Report of Creutzfeldt - Jakob Disease in the Context of COVID-19

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Abstract

Creutzfeldt-Jakob disease (CJD) is a rare, but fatal neurodegenerative disease characterized by rapidly progressive neurological deficits including cognitive impairment, personality changes, aphasia, dysphagia, ataxia, and pyramidal and/or extrapyramidal symptoms [1,2]. CJD should be suspected in patients with rapidly progressive dementia syndrome.

Since the Coronavirus disease 2019 (COVID-19) pandemic, diverse neurological complications have been observed such as stroke, encephalitis, and Guillain-Barré syndrome [3]. Moreover, there have been case reports about temporary or long-term neurological sequelae after COVID-19 vaccines, but there is no strong evidence to support these findings [4].

This is a case of rapid neurological decline secondary to sporadic CJD that occurred several weeks post both asymptomatic COVID-19 infection and recent COVID-19 mRNA booster vaccination.

Keywords: Creutzfeldt-Jakob; COVID-19; Encephalitis; Encephalopathy; Neurodegeneration

Case Presentation

A 74-year-old female presented to the emergency room for evaluation of worsening aphasia, dysphagia, and ataxia for one week.

Three weeks prior to presentation, she was admitted to the hospital for confusion. She was diagnosed with focal seizures and discharged on Levetiracetam 500 milligrams twice a day. During the same admission, she tested positive for COVID-19 via polymerase chain reaction test. She was asymptomatic and had an unremarkable chest x-ray; therefore no treatment was indicated. Two months prior to admission, she was vaccinated with the second dose of COVID-19 mRNA, and did not experience any side effects. Her chronic medical problems included prediabetes and dyslipidemia.

On presentation, her physical exam was remarkable for expressive and receptive aphasia as well as right arm and leg drift. Complete blood count and comprehensive metabolic panel were within normal limits. Computerized tomography (CT) of the head showed patchy hypodensities possibly related to mild microvascular ischemic disease, but no other acute changes were seen. Magnetic resonance imaging (MRI) of the brain revealed restricted diffusion located in the lateral and paramedian aspects of the left parietal lobe, left frontal lobe, left insular cortex and basal ganglia (figure 1). A lumbar puncture was performed due to concern for encephalitis. Cerebrospinal fluid (CSF) analysis was significant for an elevated protein level of 79 mg/dL. Infectious work-up was negative (table 1). Electroencephalograms (EEG) showed background slowing indicative of general cerebral dysfunction.

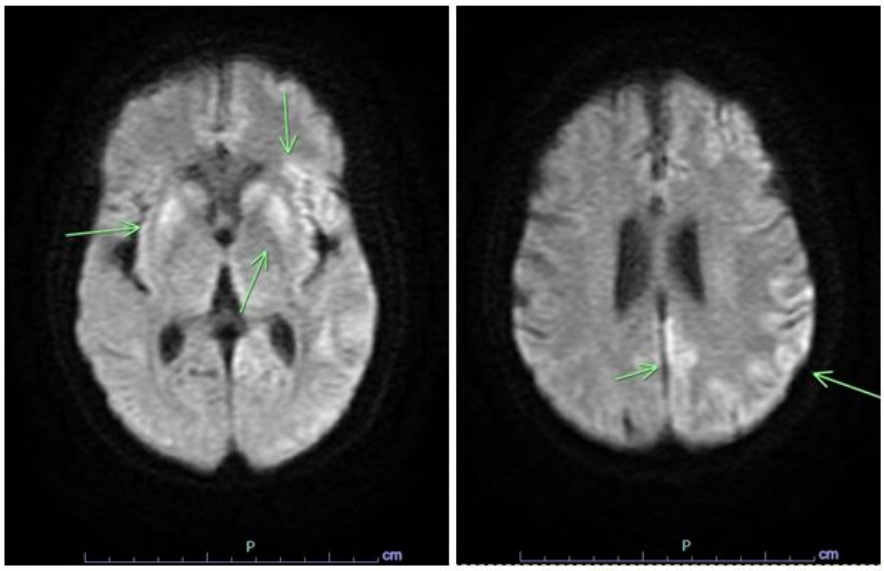

Figure 1: Brain MRI (diffusion-weighted imaging) showing restricted diffusion predominantly in the lateral and paramedian aspects of the left parietal lobe,the paramedian left frontal lobe, left insular cortex and basal ganglia bilaterally

Table 1: Relevant laboratory analysis

	Value	Reference range
Complete blood count	WBC: 9.2 × 10^9/L	3.5-10 × 10^9/L
	Neutrophils: 68.3%	40-75%
	Lymphocytes: 22.6%	20-45%
	Monocytes: 8.2%	4-12%
	Eosinophils: 0.3%	0-7%
Metabolic panel	Sodium: 141 mmol/L	135-145 mmol/L

	Potassium: 4.3 mmol/L	3.5-5.3 mmol/L
	BUN: 13 mg/dL	6-23 mg/dL
	Calcium: 9.5 mg/dL	8.6-10.4 mg/dL
	Ammonia: 17 μmol/L	11-51 μmol/L
	B12: 504 pg/mL	232-1,245 pg/mL
	Folate: 18.8 ng/mL	> 4 ng/mL
Autoimmunity	ESR: 25 mm/hr	< 29 mm/hr
	CRP: 4.3 mg/L	< 8 mg/L
	ANA: 1:80	< 1:40
	Ro/SSA, La/SSB, Smith, RNP, Scl-70, JO-1: Negative	Negative
	Anti-PR3, Anti-MPO: Negative	Negative
Serum	HIV Ab: Negative	Negative
	RPR: Negative	Negative
	Lyme Ab: Negative	Negative
CSF cell count	WBC: 1 cells/mm^3	0-5 cells/mm^3
	RBC: 8 cells/mm^3	0 cells/mm^3
CSF cytology	Rare scattered mononuclear cells, mostly benign lymphocytes	
CSF analysis	**Protein: 79 mg/dL**	15-45 mg/dL
	CSF/serum glucose ratio: 60%	50-90%
	RT-QuIC for PrP: Positive	Negative
	Protein 14-3-3: Positive	Negative
	T-tau protein: 10,077 pg/mL	0-1,149 pg/mL
CSF microbiology	Gram stain: No organism	Negative
	Culture: No growth	Negative
	AFB: No growth	Negative
	HSV 1-2: Negative	Negative
	Enterovirus: Negative	Negative
	Cryptococcal Ag: Negative	Negative
	Borrelia: Negative	Negative
CSF autoimmune panel	NMDA-R Ab, AMPA-R Ab, DPPX Ab, CASPR2-IgG, LGI1-IgG, GABA-B-R, Ab: Negative	Negative

Abnormal results are shown in bold.

Ab: antibody; AFB: acid-fast bacteria; Ag: antigen; AMPA-RAb: Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antibody; ANA: antinuclear antibody; BUN: blood urea nitrogen; CASPR2-IgG: Contactin-associated protein-like 2 immunoglobulin G; CRP: C-reactive protein; DPPX Ab: Dipeptidyl-peptidase-like protein antibody; ESR: erythrocyte sedimentation rate; GABA-B-R Ab: Gamma Aminobutyric acid receptor type B antibody; HIV: human immunodeficiency virus; HSV: herpes simplex virus; LGI1-IgG: Leucine-Rich glioma-inactivated protein 1 immunoglobulin G; MPO: myeloperoxidase; NMDA-R Ab: N-methyl-d-aspartate receptor antibody; PR3: proteinase 3; PrP: prion protein; RBC: red blood cells; RPR: rapid plasma reagin; RT-QuIC: real-time quaking-induced conversion; WBC: white blood cells

After bacterial and viral encephalitis were ruled out, the patient received intravenous immunoglobulins (IVIG) for possible autoimmune encephalitis. Due to lack of clinical response, COVID-19 encephalitis was suspected. Therefore, 1 gram of intravenous methylprednisolone was administered for 5 days. Unfortunately, her neurological

condition continued to rapidly decline and she became comatose on day 18 of her hospitalization. Ultimately, her 14-3-3 CSF assay and RT-QuIC returned positive. A diagnosis of probable sporadic CJD was made based on the Centers for Disease Control and Prevention (CDC) criteria (table 2).

Table 2: CDC's Diagnostic Criteria for Probable CJD

● Neuropsychiatric disorder plus positive RT-QuIC in CSF or other tissues
OR
● Rapidly progressive dementia; and at least two out of the following clinical features
○ Myoclonus ○ Visual or cerebellar signs ○ Pyramidal/extrapyramidal signs ○ A kinetic mutism
AND a positive result on at least one of the following laboratory tests
● Typical EEG (periodic sharp wave complexes) during an illness of any duration
● Positive 14-3-3 CSF assay in patients with a disease duration of less than 2 years
● High signal in caudate/putamen on brain MRI or at least two cortical regions (temporal, parietal, occipital) either on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR)
AND without routine investigations indicating an alternative diagnosis

The patient's family declined a biopsy to confirm the diagnosis. After family discussion, the patient was ultimately transitioned to comfort care.

Discussion

An early diagnosis of a rare disease is challenging even in the best conditions, but it amplifies during a pandemic when isolation and social distancing is mandatory [5]. The described patient developed a rapid cognitive decline along with pyramidal symptoms which are commonly seen in CJD [6]. However, her clinical decline was initially attributed to COVID-19 encephalitis rather than CJD due to her recent SARS-CoV-2 infection [7].

A considerable amount of literature has been published about different neurological manifestations associated with SARS-CoV-2. A few authors hypothesized that COVID-19 can be a possible cause of sporadic CJD or that it can accelerate the course of the underlying neurodegenerative disease [3,8]. The hypothesis is that SARS-CoV-2 can potentially induce a neuroinflammatory state that leads to misfolding and aggregation of PrP. In fact, infectious agents have been reported as a possible risk factor for neurodegenerative diseases, causing protein misfolding and aggregation in selected brain regions [9]. There is also data suggesting that

SARS-CoV-2 binds to heparin binding proteins and accelerates the aggregation of pathological amyloid proteins present in the brain [10].

Notably, the above patient also received the COVID-19 mRNA vaccine one month prior to her first neurologic symptom. A few case reports describe a potential link between CJD and COVID-19 mRNA vaccine [4,11]. This may be due to vaccine contents binding to specific proteins causing pathologic misfolding. This relationship may be coincidental, and further studies are needed in order to make a definitive conclusion.

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None.

Declaration of Interest Statement

The authors have no conflict of interest.

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