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LETTER TO THE EDITOR

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COVID-19 encephalitis and Wernicke's encephalopathy

To The Editor,

Patients with COVID-19 can present with acute encephalopathy and changes in the level of consciousness. A 74-year-old high-functioning woman was admitted after two brief syncopal episodes with eye-rolling. In addition, she reported a dry cough for 6 weeks without associated symptoms. There was no relevant past medical history and she did not drink alcohol.

Clinical examination revealed bibasal crackles on chest auscultation and oxygen desaturation on mild exertion. Glasgow Coma Scale (GCS) score was 15/15 and neurological assessment was normal. Investigations were notable for lymphocyte count of 0.51×10^9/L (1.0–4.0) and elevated C-reactive protein (CRP) at 26 mg/L (0–4). The remaining hematologic and biochemical parameters were unremarkable. Chest radiography demonstrated bilateral subpleural infiltrates. COVID-19 was confirmed by detection of SARS-CoV-2 viral nucleic acid on a nasopharyngeal swab using polymerase chain reaction (PCR) assay.

During the first week of admission, there was persistent vomiting, swinging pyrexia, and fluctuating GCS between 5/15 and 7/15. Neurological status continued to deteriorate over the next few days. On examination, she was hypomimic with symmetrical facial weakness and limitation of ocular movements in all planes but with normal pupillary size and reaction. Reflexes were brisk in the upper limbs and attenuated in the lower limbs with bilateral downgoing plantar responses. No signs of meningeal irritation were elicited. No gross peripheral nervous system (PNS) deficit was demonstrated.

Computed tomography (CT) of the head was unremarkable. CT chest demonstrated bilateral peripheral infiltrates and ground glass changes throughout both lung fields consistent with COVID-19 pneumonitis. Two magnetic resonance imaging (MRI) brain scans were subsequently performed; the first, without gadolinium, demonstrated hyperintense signal at the area postrema (medulla oblongata) raising the possibility of viral-related encephalitis (Figure 1A–D), and the second, performed a week later, with gadolinium, demonstrated significant homogenous contrast enhancement of bilateral mammillary bodies, typical of Wernicke's encephalopathy (WE) (Figure 1E–L).

Involvement of the area postrema was thought to explain persistent vomiting. Cerebrospinal fluid (CSF) examination revealed normal opening pressure, elevated protein level of 0.78 g/L (0.2–0.4), normal glucose and leukocyte count, sterile cultures, and negative serology, including PCR for SARS-CoV-2. Nerve conduction studies (NCS) were unequivocal for acute demyelination (Table 1). At the height of neurological collapse, laboratory investigations revealed thrombocytopenia with platelet count dropping from 268×10^9 to 60×10^9/L (150–450), hyperferritinemia at 1950 µg/L (30–470), elevated lactate dehydrogenase at 347 U/L (135–210) and a modest elevation in the CRP at 77 mg/L; all of these being cited markers of cytokine release syndrome or "cytokine storm." Aquaporin-4, antimyelin oligodendrocyte glycoprotein, and antiganglioside antibodies were negative.

The thiamine level was found low at 63.9 nmol/L (70–200). Intravenous vitamin B complexes were empirically administered alongside nasogastric feeding to prevent a further nutritional deficit. Five days of pulsed intravenous methylprednisolone (500 mg/day) and immunoglobulin (400 mg/kg/day) were also trialed in view of a possible diagnosis of acute inflammatory demyelinating polyneuropathy (AIDP).

Repeat MRI with gadolinium 3 weeks later demonstrated reduction in abnormal T2 and flair hyperintensities previously visualized and decreased contrast uptake in the mammillary bodies (Figure 1M–T). Seven weeks after readmission, the patient remains disoriented in time and space but communicates articulately, follows simple commands, has normal ocular and facial movements, has full power in the upper limbs, and is beginning to mobilize with assistance.

This case demonstrates encephalitic involvement of the vomiting center in the brainstem (area postrema) which induced hyperemesis and caused malnourishment and metabolic derangement. This progressed to encephalopathy and pseudo-comatose state, both likely related to viral angiotensin-converting enzyme 2 (ACE2) binding.[1]

Raised CSF protein and sensorimotor neuropathy (with evidence of demyelination on NCS) initially raised the suspicion of AIDP. This has been described post-COVID-19 which led to the trial of treatment with intravenous corticosteroid and immunoglobulin.[2] In retrospect, WE and dry beriberi caused by thiamine deficiency were more plausible diagnoses, supported by neuroradiological features, negative detection of antibodies in CSF, and rapid response to treatment.

It has been reported that neurological features of WE can mimic those of AIDP with CSF albuminocytologic dissociation and sensorimotor polyneuropathy.[3,4] Thiamine is a key enzymatic cofactor in the Krebs cycle and is required for maintaining cerebral energy homeostasis. Starvation or dietary insufficiency can deplete thiamine reserves within 2–3 weeks.[4] Thiamine deficiency decreases enzyme activity involved in aerobic glucose metabolism, resulting in the accumulation of lactic acid. Lactic acidosis is associated with increased expression of aquaporin-4 which in turn leads to swelling of glial cells and release of cytokines and chemokines, causing inflammation, oxidative stress, and cell apoptosis.[5] In COVID-19, where hypoxia is

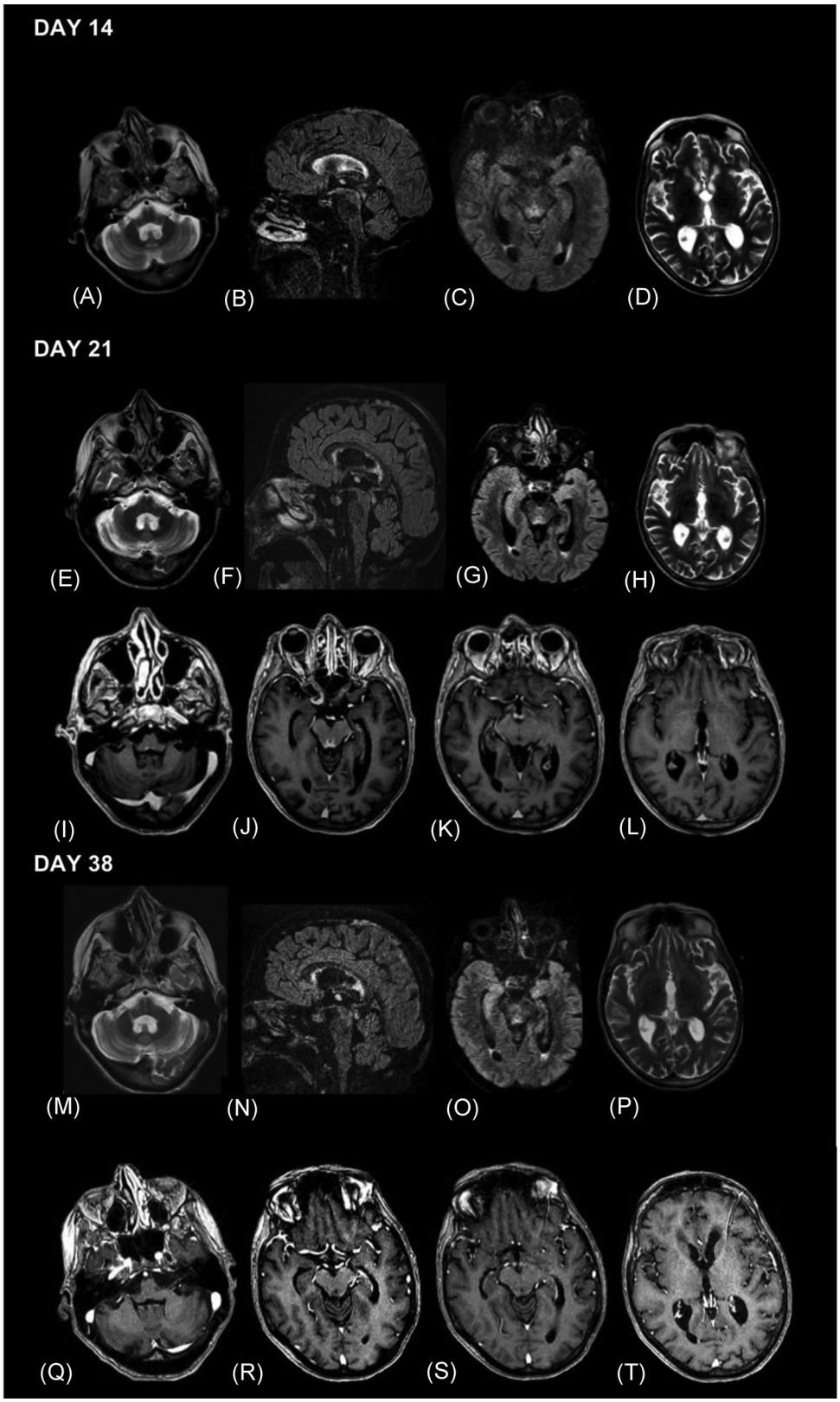

FIGURE 1 (See caption on next page)

TABLE 1 Nerve conduction studies demonstrated universally absent sensory responses despite medium to relatively high levels of electrical stimulation

Sensory Studies				
Nerve	Amp (uV)	Lat (ms)	Distance (mm)	NCV (m/s)
R. median F2—wrist	Absent	–		
L. median F2—wrist	Absent	–		
R. ulnar F5—wrist	Absent	–		
L. ulnar F5—wrist	Absent	–		
R. superficial radial	Absent	–		
L. superficial radial	Absent	–		
R. sural	Absent	–		
L. sural	Absent	–		
Motor studies				
Nerve—muscle	DML (ms)	CMAP (mV)	min F-lat (ms)	% freq
L. median—APB wrist	7.1	2.3	Absent	–
Elbow	16.6	0.4	dispersed	
MCV median L. forearm	24.3 m/s			
R. c. peroneal—EDB ankle	Absent	–	Absent	–
knee	Absent	–		
MCV per R. leg	–m/s			
L. c. peroneal—EDB ankle	Absent	–	Absent	–
Knee	Absent	–		
MCV per L. leg	–m/s			

Note: Compound muscle action potential (CMAP) of bilateral common peroneal muscles were absent as are the corresponding F waves. Distal demyelination is demonstrated by the moderately increased distal motor latencies in the abductor pollicis brevis muscle. Left median forearm motor conduction velocity was reduced with absent corresponding F waves. Findings were suggestive of an underlying moderately severe recent-onset acute primary demyelinating polyradiculoneuropathy.

Abbreviations: Amp, amplitude; CMAP, compound muscle action potential; APB, abductor pollicis brevis; c., common; DML, distal muscle latency; EDB, extensor digitorum brevis; freq, frequency; L., left; Lat, latency; MCV, motor conduction velocity; NCV, nerve conduction velocity; R., right.

common, this inflammatory cascade may further contribute to hypoxic injury of the central nervous system.

Although vomiting and nutritional insufficiency were key to the development of WE and dry beriberi in our patient, active COVID-19 may have contributed to the demyelinating process. Multiple mechanisms of neuronal injury by coronaviruses have been described; these include hypoxia and immune-mediated injury.[6] We postulate that the combination of these mechanisms and viral invasion of glial cells may lead to significant neuroinflammation and subsequent blood–brain barrier (BBB) breakdown. This is likely mediated by ACE2-viral binding with either direct BBB entry through invasion of glial cells or indirect entry via infiltration of BBB endothelial cells (ACE2 being abundant in both cell types). These processes are thought to be mirrored in the PNS with resultant inflammation and demyelination.

We lay emphasis upon thorough neurological assessment and prompt neuroimaging for COVID-19 patients who present with confusion and altered mental status. We highlight the inherent risks of malnutrition and metabolic encephalopathy among COVID-19 patients with protracted vomiting or prolonged illness.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

All authors cared for the patient. All authors contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript. Elena Boyd and Hatice Tuzlali were responsible for the collation and interpretation of the neuroradiological images. Constantinos G. Missouris oversaw the project.

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FIGURE 1 Area postrema hyperintensities on T2-weighed axial (A) and sagittal fluid-attenuated inversion recovery (FLAIR) imaging (B), midbrain tectal hyperintensities on both sagittal and axial FLAIR imaging (B and C) and on the bilateral medial thalami, around the third ventricle, on axial T2W images (D) were seen 21 days after first COVID-19 diagnosis. Five days later a repeat brain magnetic resonance imaging scan with contrast showed partial resolution of the area postrema T2 hyperintensities, as seen in axial T2W images (E) and sagittal FLAIR images (F) but with mild contrast enhancement in this area on axial T1 weighted imaging (I). T2 and FLAIR hyperintensities were less evident in the midbrain tectal plate (G) and medial thalami (H), respectively. However, there was significant contrast enhancement of these areas (J–L) as well as bilateral mamillary bodies (K). After treatment, 38 days post-COVID-19 diagnosis, all the previously described signal abnormalities regressed (M, N, and P) except for mild T2 hyperintensity of the tectal plate. (N and O) The contrast enhancement of the previously affected areas regressed (Q–T) with the mild persisting enhancement of the tectal plate (R) and mamillary bodies (S)

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