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# Post-COVID-19 acute disseminated encephalomyelitis: Case report and review of the literature

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ABSTRACT

*Background:* Our understanding of the spectrum of neurological manifestations associated with COVID-19 keeps evolving. Reports of life-threatening neurological complications, such as acute disseminated encephalomyelitis (ADEM), are alarmingly growing in number.

*Case presentation:* We report a 42 years old previously healthy man who presented with left visual loss and cognition deterioration, manifesting at least ten days after infection with SARS-CoV-2. Serological work-up for potential immunological markers (i.e., antibodies against aquaporin-4 and myelin oligodendrocyte glycoprotein) were negative. Magnetic resonance imaging revealed multiple bilateral and asymmetrical lesions in the brainstem, cortical, juxtacortical, and periventricular regions, with surrounding edema. Post-contrast sequences demonstrated punctate, ring, and open ring enhancement patterns. Methylprednisolone pulse therapy was initiated for the patient, and he was placed on rituximab. After one month, his clinical symptoms had resolved, and his cognitive function was normal.

*Conclusions:* We conducted an extensive literature search, and COVID-19-associated ADEM cases reported thus far were identified and reviewed. ADEM often occurs in a post-infectious fashion; however, it is unclear how SARS-CoV-2 infection can trigger such rapidly progressive episodes of encephalopathy and demyelination. Nevertheless, considering the alarming number of cases of ADEM developing after SARS-CoV-2 infection, neurologists should consider this severe phenotype of COVID-19 neurological complication in mind, enabling prompt therapeutic interventions to be made.

## Introduction

With the ongoing pandemic of Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, significant concerns were raised regarding the spectrum of neurological manifestations associated with this infection. A wide variety of such complications can occur in COVID-19 patients, with various pathologies and degrees of severity, due to either direct or indirect involvement of the central nervous system (CNS) (Al-Sarraj et al., 2021). There are numerous reports of CNS immune-mediated conditions; the underlying pathogenesis is not clear yet.

Several cases of acute disseminated encephalomyelitis (ADEM; an immune-mediated demyelinating disorder of the CNS) after infection with SARS-CoV-2 have been reported (reviewed in Table 1). ADEM is more frequently observed in children, especially after infection and reports have shown that ADEM might be associated with vaccination lenges. Although ADEM and AE have similar presentations, symptoms develop more rapidly in ADEM (McGetrick et al., 2021).

We describe the case of an adult patient who developed an ADEM episode shortly after he was infected with SARS-CoV-2. We conducted an extensive search of relevant literature and summarized the existing data on post-infectious ADEM in the context of COVID-19.

## Case presentation

In early January 2021, a previously healthy 42-year-old man presented with visual loss in the left eye, bilateral ptosis, drowsiness, and declined cognition from three days before admission. He had been quarantined in a non-healthcare setting from 10 days before the onset of his neurological symptoms for a history of low-grade fever, dyspnea, cough, and myalgia. Nasopharyngeal swab polymerase chain reaction (PCR) was positive for SARS-CoV-2 and negative for influenza H1N1.

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**Table 1**
Demographic, clinical, radiological of cases with acute disseminated encephalomyelitis associated with COVID-19, along with their treatments and outcomes.

| Case | Age/ Sex | publication date | country of study | ADEM symptoms | MRI finding | Treatment | Outcome |
|---|---|---|---|---|---|---|---|
| 1 Novi et al. (2020) | 64/F | September 2020 | Italy | Severe visual loss<br>Sensory deficit<br>Headache<br>Hyperreflexia<br>Babinski sign<br>Right abdominal sensory level<br>Irritability | Multiple T1 post-Gd enhancing lesions of the brain, associated with a single spinal cord lesion at the T8 level and with bilateral optic nerve enhancement | High-dose steroids<br>IVIG | Significant improvement in visual symptoms<br>Reduced number of Gd-enhancing lesions in follow-up brainMRI |
| 2 Virhammar et al. (2020) ANE | 55/F | September 2020 | Sweden | Stupor<br>Multifocal myoclonus | Symmetrical FLAIR hyperintensities signal symmetrically in central thalami, subinsular regions and thalami, medial temporal lobes, and brain stem, consistent with ANE | Acyclovir<br>IVIG<br>Plasma exchange | The patient clinically improved |
| 3 Dixon et al. (2020) ANE | 59/F | September 2020 | United Kingdom | Seizure (GTCS)<br>Reduced level of consciousness<br>Unreactive left pupil | Brain stem swelling, symmetrical hemorrhagic lesions in the brain stem, amygdalae, putamina, and thalamic nuclei | High-dose steroids<br>Levetiracetam<br>Acyclovir<br>Ceftriaxone<br>Amoxicillin<br>Clarithromycin | Died |
| 4 Parsons et al. (2020) | 51/F | May 2020 | USA | Unresponsiveness<br>Depressed deep tendon reflexes<br>Mute plantar responses<br>Flaccid muscle tone | Small Gd-enhancing lesion in the left frontal lobe at the gray-white interface and FLAIR hyperintensities in the deep hemispheric, periventricular and juxtacortical white matter | High-dose steroids IVIG | Fully oriented |
| 5 de Miranda Henriques-Souza et al. (2021) | 12/F | October 2020 | Brazil | Flaccid tetraplegia<br>Deep areflexia<br>Tingling and numbness in the inferior limbs | Extensive bilateral and symmetric restricted diffusion involving the subcortical and deep white matter<br>Focal hyperintense T2 FLAIR lesion in the splenium of the corpus callosum with restricted diffusion | High-dose steroids | Partial improvement |
| 6 Langley et al. (2020) | 53/M | November 2020 | United Kingdom | Hypotonia<br>Agitation | Bilateral multiple hyperintense lesions within the subcortical and deep white matter of the frontoparietal lobes<br>Small amount of IVH within the occipital horns of the lateral ventricles | High-dose steroids | The patient clinically improved |
| 7 Lopes et al. (2020) | 59/F | October2020 | Brazil | Reduced level of consciousness<br>Asymmetric flexor motor responses<br>Hyporeflexia | Multiple bilateral focal areas of signal abnormalities in the cerebral and cerebellar white matter | Hydroxychloroquine<br>Broad-spectrum antibiotics | Died |

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**Table 1** (*continued*)

| Case | Age/ Sex | publication date | country of study | ADEM symptoms | MRI finding | Treatment | Outcome |
|---|---|---|---|---|---|---|---|
| 8 Lopes et al. (2020) | 41/M | October2020 | Brazil | Reduced level of consciousness<br>Four-limb weakness<br>Blunted affect<br>Poor verbal interaction | Focal lesions located in the centrum semiovale, bilaterally, right thalamus, globus pallidus bilaterally and anterior limb of internal capsule, characterized by hyperintensity on axial FLAIR images, high signal on DWI and apparent diffusion coefficient, representing diffusion facilitation | Not reported | Fully alert and cooperative patient, with mild attentional and executive dysfunction |
| 9 Hussein et al. (2020) | 55/F | September 2020 | USA | Reduced level of consciousness<br>Seizure<br>Generalized weakness | Mild asymmetric FLAIR hyperintensities in the left>right cerebral cortex, thalami, the left sub splenial region,<br>the left subcortical optic radiations and the mid pons | Levetiracetam<br>Lacosamide<br>Topiramate<br>IVIG<br>High-dose steroids<br>Plasmapheresis | The patient clinically and electrographically improved |
| 10 Umapathi et al. (2020) | 59/M | September 2020 | Singapore | Drowsy<br>Roving eye movements<br>Transient ocular flutter | Multiple discrete hyperintense foci in the periventricular and deep white matter bilaterally, with foci in the temporal region, subcortical white matter as well as the forceps minor | Convalescent plasma<br>IVIG | He was able to open eyes spontaneously, track visually and smile meaningfully. However, he had no coherent volitional<br>motor and verbal response to the environment |
| 11 Reichard et al. (2020) | 71/M | May 2020 | USA | Not reported | Not reported | High-dose steroids<br>Vasopressor | Died |
| 12 Zhang et al. (2020) | 40/F | April 2020 | USA | Dysphagia<br>Dysarthria<br>Encephalopathy | Extensive patchy areas of abnormal signal involving bilateral frontoparietal white matter, anterior temporal lobes, basal ganglia, external capsules, and thalami | Hydroxychloroquine<br>Ceftriaxone<br>IVIG | The patient clinically improved |
| 13 Shahmirzaei and Naser Moghadasi (2021) | 30/M | January 2021 | Iran | Ataxia<br>Confusion | Multiple enhanced lesion | High-dose steroids<br>Rituximab | The patient clinically improved |
| 14 McCuddy et al. (2020) | 37/F | 2020 | USA | Plegic in legs bilaterally<br>Symmetric weakness in the upper extremity | Multiple T2 hyperintense lesions with restricted diffusion involving the corpus callosum, bilateral cerebral white matter, right pons and in the bilateral ventral medulla | Decadron<br>Hydroxychloroquine Zinc<br>Convalescent plasma | Partial improvement |
| 15 McCuddy et al. (2020) | 56/M | 2020 | USA | Unresponsive,<br>Eyes with leftward deviation,<br>No spontaneous limb movements, Reflexes reduced | Several T2 hyperintense lesions, many with restricted diffusion, in cerebral white matter<br>No hemorrhage | Solumedrol<br>IVIG<br>Convalescent plasma | Clinically, not opening eyes, unresponsive<br>Remains on ventilator with tracheostomy |
| 16 McCuddy et al. (2020) | 70/F | 2020 | USA | severe diffuse weakness<br>Unresponsive to verbal stimuli<br>Withdraws to pain slightly | Several T2 hyperintense lesions, most with restricted diffusion, in deep cerebral white matter<br>Minimum enhancement and no hemorrhage | Solumedrol<br>IVIG<br>Convalescent plasma | Spontaneously opens eyes<br>decorticate posturing in upper extremity<br>Withdraws lower extremity to stimuli<br>Weaning from the ventilator |

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**Table 1** (*continued*)

| Case | Age/ Sex | publication date | country of study | ADEM symptoms | MRI finding | Treatment | Outcome |
|---|---|---|---|---|---|---|---|
| 17 AHL<br>Handa et al. (2020) | 33/M | September 2020 | India | Four-limb weakness<br>Seizure (GTCS)<br>DTR: absent<br>Babinski sign | Symmetrical FLAIR hyperintensities involving bilateral subcortical fronto-parietal lobes, splenium of corpus callosum, medulla and visualised cervical cord with petechial haemorrhages and evidence of diffusion restriction involving splenium of corpus callosum | Acyclovir<br>Ceftriaxone<br>Lacosamide<br>High-dose steroids | Died |
| 18 Manzo et al. (2021) | 6/M | May 2021 | Italy | Seizure (GTCS) | T2-FLAIR hyperintense lesions in the right cerebellar hemisphere, cortical-subcortical cuneus gyrus of the right parietal lobe, left side of the corpus callosum and corona radiata, cortical-subcortical inferior left parietal gyrus | High-dose steroids | The patient clinically improved |
| 19 AHL<br>Varadan et al. (2021) | 46/M | February 2021 | India | Headache<br>Reduced level of consciousness<br>Loss of power in the left limbs<br>Left facial nerve palsy | Hyperintense white matter lesions in bilateral frontal, parietal lobes, left thalamus, left cerebral peduncle, and medulla T2W and FLAIR, hypointense onT1W<br>Pre and postcontrast of lesions show patchy, rim enhancement with central nonenhancing component | High-dose steroids | Died |
| 20 McLendon et al. (2021) | 17-month /F | March 2021 | USA | Irritability<br>Weakness of upper extremities<br>Ataxia<br>Neck stiffness<br>Brudzinski's sign | Revealed multifocal hyperintense FLAIR signals in bilateral subcortical and periventricular white matter without contrast enhancement | IVIG<br>High-dose steroids | The patient clinically improved |
| 21 ANHLE<br>Alqahtani et al. (2021) | 59/M | June 2021 | Saudi Arabia | Reduced level of consciousness<br>Absence of some brainstem reflexes | Extensive brain abnormality predominantly involving the deep white matter with micro haemorrhages | Health guidelines of Saudi Ministry | Died |
| 22 ANHLE<br>Alqahtani et al. (2021) | 47/F | June 2021 | Saudi Arabia | Reduced level of consciousness<br>Blurred vision<br>Abnormal movement of the right upper limb and left lower limb | Diffuse petechial hemorrhages especially in the basal ganglia that is compatible with diffuse necrotizing leukoencephalitis | Not reported | Coma |

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**Table 1** (*continued*)

| Case | Age/ Sex | publication date | country of study | ADEM symptoms | MRI finding | Treatment | Outcome |
|---|---|---|---|---|---|---|---|
| 23 Kumar et al. (2020) | 35/F | September 2020 | USA | Gait instability<br>Symmetric distal neuropathy<br>Reduced level of consciousness | Hemispheric white matter signal in juxtacortical regions extending to anteromedial temporal lobes<br>Symmetric periventricular white matter FLAIR hyperintensities involving bilateral cerebral peduncles with mild diffusion restriction | High-dose steroids<br>IVIG<br>plasma exchange | She had not improved, and was transferred to a long term care facility |
| 24 AHL<br>Haqiqi et al. (2021) | 56/F | January 2021 | United Kingdom | Reduced level of consciousness | Extensive symmetrical FLAIR abnormal signal throughout the white matter bilaterally with hemorrhage compatible with haemorrhagic leukoencephalitis | Anticoagulation<br>Antihypertensive | The patient neurological condition has remained stable<br>He discharged to a neurorehabilitation center. |
| 25 AHL<br>Yong et al. (2020) | 61/M | July 2020 | Singapore | Flaccid tetraplegia<br>Absent plantar reflexes | Asymmetrical, multifocal lesions in the subcortical white matter of bilateral cerebral hemispheres, cortex, Bilateral thalami, and cerebellar hemispheres, petechial hemorrhage and vasogenic edema within the lesions<br>10 mm rightward midline shift | Remdesivir<br>Plasma exchange<br>IVIG | The patient clinically improved |
| 26 Abdi et al. (2020) | 58/M | June 2020 | Iran | Reduced level of consciousness<br>Inability to walk<br>Status epilepticus | Diffuse confluent white matter hyperintensity on FLAIR, particularly at the left-side without prominent enhancement on T1 | High-dose steroids | Died |
| 27 Walker et al. (2021) | 51/F | April 2021 | USA | Increased seizure activity<br>Incontinence<br>Aphasia | Not reported | Remdesivir | Died |
| 28 Walker et al. (2021) | 64/M | April 2021 | USA | Nonresponsive with a fixed and dilated right pupil | Not reported | Remdesivir<br>Convalescent plasma<br>Corticosteroids | Died |
| 29<br>Delamarre et al. (2020) | 51/M | September 2020 | France | Unresponsive coma<br>Pyramidal syndrome<br>Right-sided sixth nerve palsy<br>No corneal reflex | Diffuse hyperintense lesions on FLAIR images without Gd-enhanced lesions | High-dose steroids IVIG | The patient showed complete motor recovery |
| 30<br>Karapanayiotides et al. (2020) | 57/M | October 2020 | Greece | Reduced level of consciousness<br>Hyperreflexia<br>Blunted vestibulo-ocular reflexes | Concentric demyelination pattern | Azithromycin<br>Hydroxychloroquine<br>Ritonavir Interleukin-1 antagonist | The patient recovered, and 1 month later, he only had moderate tetraparesis |
| 31 Poyiadji et al. (2020)<br>ANE | ?/F | March 2020 | USA | Altered mental status | hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions | IVIG | Not reported |

*Abbreviations:* Gd, Gadolinium; ANE, Acute necrotizing encephalopathy; AHL, Acute hemorrhagic leukoencephalitis/leukoencephalomyelitis; ANHLE, Acute necrotic hemorrhagic leukoencephalitis; GTCS, Generalized tonic-clonic seizure; IVIG, intravenous immunoglobulin G; IVH, Intraventricular hemorrhage; DWI, Diffusion weighted imaging.

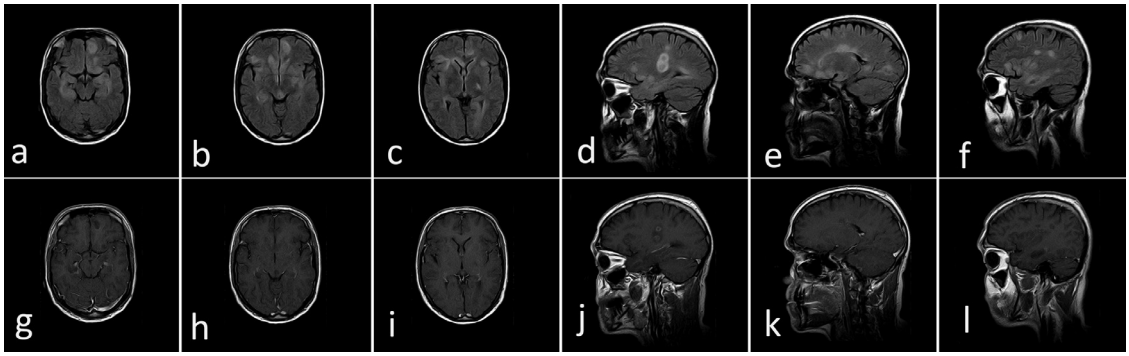


**Fig. 1.** Fluid-attenuated inversion recovery images (a–f) of the brain showing multiple high-signal lesion in the brainstem, cortical, juxtacortical, and periventricular areas. Post-contrast T1-weighted sequences (g–l) showing enhanced lesion as target sign with low-signal dot in the center of lesion.

Upon physical examination, he was not febrile, and his vital signs were stable. The patient was lethargic and irritable. His-left visual acuity was 20/50; reflex afferent papillary defect in the corresponding eye was 3+. Bilateral ptosis, more prominent in the left side, was detected. There was mild paraparesis in the lower extremities (4/5). Sensory and cerebellar functions, deep tendon reflexes, and plantar reflexes were normal. Results from optical coherence tomography (OCT) performed by an ophthalmologist were normal.

Electrolytes, white blood cells, hemoglobin, C-reactive protein, transaminases, Serum creatinine levels were within the normal range, as were his TSH, T3, and FT4 levels.

Additional tests showed negative neuromyelitis Optica antibody (NMO-IgG) and negative myelin oligodendrocyte glycoprotein antibody (MOG-IgG) results.

Brain magnetic resonance imaging (MRI) sequences were obtained. Multiple bilateral and asymmetrical lesions were observed in the brainstem, cortical, juxtacortical, and periventricular regions, appearing as hyperintensities with surrounding edema on T2-weighted and Fluid-attenuated inversion recovery (FLAIR) images. Post-contrast T1-weighted sequences revealed punctate, ring, and open ring enhancement patterns. Electroencephalogram (EEG) showed generalized slowing with no epileptiform discharge.

The patient underwent methylprednisolone pulse therapy for five days (1 g/day), followed by two doses of rituximab infusion (1 g/infusion; with a two-week interval). After one month, the patient's clinical symptoms resolved, visual acuity was normal (10/10), ptosis and mental status evaluation were also normal.

## Discussion

Adding to the growing body of evidence, we reported a case of post-COVID-19 ADEM with manifestations of cognitive deficits and visual loss in a 42-year-old man. Although this demyelinating disorder of the CNS tends to occur after infections, an exact, causal relationship between infections and ADEM is yet to be determined (Pohl et al., 2016). The absence of NMO-IgG and MOG-IgG excluded the probability of Neuromyelitis optica spectrum disorder and MOG-associated Disease, resulting in ADEM diagnosis. Unlike the predominance of ADEM occurrence in children, our patient, similar to most reported cases of COVID-19-associated ADEM, was a middle-aged individual.

Our extensive search of the existing literature on COVID-19 and associated ADEM yielded 31 cases; data extracted from those cases are presented in Table 1. As interpreted from Table 1, there was no gender predominance among the cases (16 females, 15 males). Most patients (90.3%; 28/31) were adults with an average age of 52.3 years. Only a few patients had severe COVID-19-associated symptoms and required intensive care. 55.8% (17/31) had reduced levels of consciousness and a decreased GCS. Muscle weakness or decreased muscle tone was observed in 35.4% (11/31); 4 patients (Novi et al., 2020, Langley et al., 2020, Shahmirzaei and Naser Moghadasi, 2021, McCuddy et al., 2020) developed seizures, and the frequency of seizures was increased in one patient who had seizures before COVID-19 infection (Yong et al., 2020). In addition to our case, visual impairments were reported in two patients (Tenembaum et al., 2002, Varadan et al., 2021). MRI findings of these patients showed multiple lesions in various regions of the CNS Fig. 1.

Different outcomes ensued with the treatments applied in the reported cases. In 58% (18/31) of cases, symptoms improvement and MRI lesions reduction were achieved. Unfortunately, 25% died. Others showed no progression of their symptoms. One patient's treatment outcome was not mentioned (Karapanayiotides et al., 2020). The neurological manifestations associated with ADEM after the COVID-19 course can significantly increase morbidity and mortality and can multiple the hospitalization time. Although corticosteroids can be beneficial in the resolution of symptoms in ADEM patients, prescription of corticosteroids should be done with caution as it can increase the risk of increased viral replication (McCuddy et al., 2020).

It is notable that while COVID-19-associated ADEM patients predominantly presented with reduced level of consciousness and muscle weakness, a review shows that the most common symptoms in patients with COVID-19-associated autoimmune encephalitis are altered mental status, seizures and ataxia (Payus et al., 2021).

In conclusion, given the significant number of ADEM cases associated with SARS-CoV-2 infection reviewed above, neurologists should bear in mind severe neurological complications that might occur after an unfortunate COVID-19 infection and promptly take action to prevent further potential damages.

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