

# Acute disseminated encephalomyelitis (ADEM) associated with COVID-19

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## SUMMARY

A 53-year-old man admitted to the critical care secondary to respiratory failure due to COVID-19 developed agitation and global hypotonia. Brain MRI revealed bilateral hyperintense lesions throughout the brain and cerebrospinal fluid identified oligoclonal bands. Intravenous high-dose glucocorticoids were administered followed by an oral tapering dose and the patient clinically improved. Acute disseminated encephalomyelitis should be considered in patients with COVID-19 who present with altered mentation and polyfocal neurological deficits.

## BACKGROUND

Neurological disturbance is commonly encountered in critically unwell patients and has been widely reported during the current COVID-19 pandemic.<sup>1 2</sup> A spectrum of encephalopathic features fall under the umbrella of 'delirium' and may include somnolence, confusion and agitation requiring sedation. In the critical care environment, where clinical neurological assessment is challenging, these features have the potential to mask an underlying inflammatory central nervous system (CNS) syndrome.

Acute disseminated encephalomyelitis (ADEM) is a rare auto-immune demyelinating disorder with an incidence in the UK of 0.23/100 000.<sup>3</sup> The condition is typically triggered by viral infections and leads to a rapid onset of multifocal neurological deficits. An emerging body of evidence has described ADEM in patients with COVID-19.<sup>1 4</sup>

Here we describe a case of ADEM occurring alongside COVID-19 pneumonia in a 53-year man in critical care as a reminder for clinicians to be aware of this potentially treatable condition. We advocate increasing the suspicion for neuroinflammatory syndromes and a low threshold for early neuroimaging where this is feasible.

## CASE PRESENTATION

A previously well 53-year-old man presented to a London hospital after 8 days of cough, shortness of breath, fevers, myalgia and malaise. He was SARS-CoV-2 PCR positive on nasopharyngeal swab. Over the first 24 hours his respiratory function deteriorated rapidly and was intubated and admitted to critical care the following day.

He was intubated for 29 days before undergoing a tracheostomy. His critical care admission was complicated by a tension pneumothorax, bilateral DVTs and the development of PICC line sepsis on day 36 (blood cultures grew *Serratia marcescens*).

He developed an acute kidney injury and required 12 days of continuous veno-venous hemofiltration. On day 43 he received a 3-day course of intravenous methylprednisolone (1g followed by two 500 µg doses). This was in response to overwhelming sepsis with hypotension and deteriorating gas exchange. There was no suspicion of a neuroinflammatory syndrome at this stage.

Throughout this initial period, he remained agitated and required high doses of multimodal sedation (clonidine, fentanyl and propofol infusions). Early attempts at sedation weans failed due to tachypnoea and persistent cough impeding ventilator synchronisation.

Sedation was significantly weaned on day 54, at which point he underwent neurological examination. His eyes opened spontaneously with pupils equal and reactive to light. He exhibited a right gaze preference with preservation of a normal doll's eye reflex. There was no verbal response to pain, and motor response was limited to right-hand twitching. He was globally hypotonic and no limb reflexes could be exhibited bilaterally.

## INVESTIGATIONS

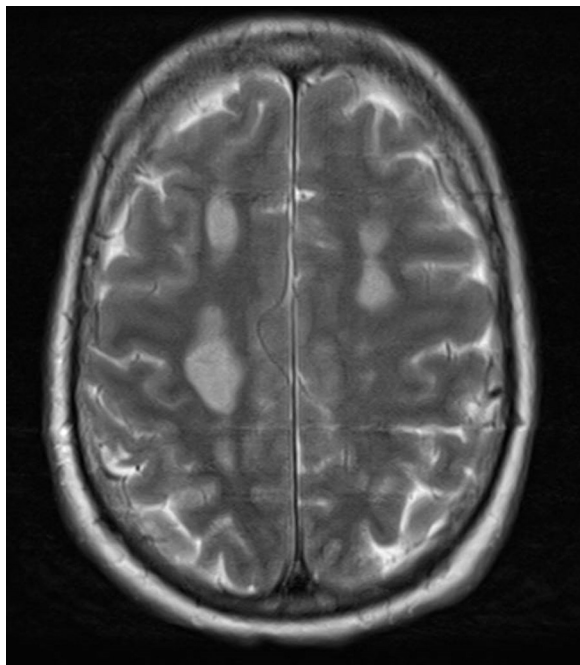
An MRI was performed to look for a cause of persistent low GCS (Glasgow Coma Score) and hypotonia following the sedation wean. MRI of the brain and orbits with gadolinium showed multiple hyperintense lesions within the subcortical and deep white matter of the frontoparietal lobes bilaterally (figure 1). These lesions were hyperintense on diffusion-weighted imaging, with restricted diffusion centrally. On the fluid-attenuated inversion recovery (FLAIR) sequence there was sulcal hyperintensity within the parieto-occipital lobes and to a lesser extent in the frontal sulci. No pathological leptomeningeal enhancement was demonstrated after gadolinium contrast. There was a small amount of intraventricular haemorrhage within the occipital horns of the lateral ventricles. Susceptibility-weighted imaging sequences showed evidence of parenchymal microhaemorrhages seen superficially in several parietal gyri, bilateral superior frontal lobes and the right occipital lobe. There was no evidence of aneurysm.

Electrolytes, bone profile, transaminases were unremarkable. C reactive protein was elevated 35.6 mg/L (0–5 mg/L); however, the white cell count was normal. Mycoplasma IgG was positive with negative IgM, suggesting past infection. Galactomannan and Beta D glucan serology were negative. D-dimer was elevated at 4460 µg/L fibrinogen equivalent units (FEU) (0–550 µg/L).



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**Figure 1** MRI brain, T2-weighted sequence, on day 46 of admission demonstrating asymmetrical and bilateral hyperintense lesions within the deep white matter.

Oligoclonal bands were detected in both the cerebrospinal fluid (CSF) and serum. CSF bacterial culture, protein and neurological viral PCR panel (adenovirus, cytomegalovirus, Epstein-Barr virus, Herpes simplex virus, Varicella zoster virus, John Cunningham virus) were all unremarkable. Electroencephalogram (EEG) showed diffuse slowing with some transient sharp theta waves detected in the centro-temporal region. Visual assessment revealed reduced acuity 6/60 in the right eye and 6/48 in the left eye. Ishihara test demonstrated marked colour deficit in the right eye. Both optical discs were unremarkable on fundoscopic examination.

### DIFFERENTIAL DIAGNOSIS

Delirium associated with critical illness is a commonly encountered but poorly understood phenomenon. It is characterised by diffuse neurological dysfunction secondary to significant organ dysfunction or infection elsewhere in the body. Clinical presentation may range from somnolence and stupor to agitation and is generally self-limiting.<sup>5</sup> Importantly, there are no specific biomarkers and it remains a clinical diagnosis. Common correctable factors should be sought and include hypoxia, drugs, toxins and metabolic derangement such as uremic and hepatic encephalopathy.<sup>6</sup>

In this case, the combination of improving respiratory and renal functions without a corresponding improvement in mentation alerted doctors to the possibility of a distinct cerebral process. In a feverish patient, this differential is broad, but the presence of focal neurology such as the hemiparesis observed in this patient should raise suspicion of a time-critical diagnosis such as cerebral abscess or encephalitis and warrants urgent neuro-imaging and lumbar puncture.

COVID-19 is also well documented to induce a hypercoagulable state, with an increased risk of venous and arterial thromboembolism.<sup>7</sup> There is an elevated risk of stroke, which appears to be significantly higher in COVID-19 compared with viral influenza.<sup>8</sup> The preservation of the doll's eye reflex in this case

implies an intact vestibulo-ocular pathway and points away from posterior circulation stroke as a cause of low GCS.

In this case, assessment of mental status was confounded by the use of sedatives used to treat the patient's agitation and promote ventilation synchronisation—as is ubiquitous on the critical care unit. Regular trials of sedation wean—even if unsuccessful at achieving their primary goal—may provide important information such as unblinding motor deficits. Although the frequency of these weans must be balanced against the risk of injury and self-extubating.

EEG may be helpful in critically unwell patients with unexplained impaired GCS primarily in order to rule out non-convulsive status epilepticus. When neuroimaging is unrevealing, EEG also serves to provide a sensitive (although non-specific) marker of cerebral dysfunction as demonstrated in this case.<sup>9 10</sup>

### TREATMENT

The patient was diagnosed with ADEM on day 59 and received 3 days of intravenous methylprednisolone 1g followed by a weaning course of prednisolone, starting at 60mg/day and reducing by 10mg/week until on a maintenance dose of 20mg.

### OUTCOME AND FOLLOW-UP

The patient clinically improved, enabling further sedation weans. Ten days after diagnosis—having completed 3 days of intravenous methylprednisolone and 4 days of 60mg of prednisolone—he was significantly more alert, able to follow one-step commands and speak in short sentences. His upper and lower limbs moved spontaneously; however, there was no withdrawal to pain in the left upper limb and only minimal movement in the left lower limb. Plantar reflexes were mute on the left and flexor on the right. His hemiparesis improved incrementally with inpatient rehabilitation over the next 2 months. His rehabilitation was complicated by postural hypotension and syncopal episodes secondary to severe deconditioning.

Two weeks after diagnosis, follow-up MRI demonstrated evolution of the lesions, with peripheral restricted diffusion and central cavitation. No new lesions were identified.

At the time of discharge to a neurorehabilitation unit, power in his left arm remained weak, Medical Research Council (MRC) grade 3/5 at the shoulder, elbow and wrists. His lower limb power was grade 5/5 bilaterally.

### DISCUSSION

#### Neurology and COVID-19

Neurological associations of COVID-19 are being increasingly described during the ongoing pandemic, which at the time of writing in August 2020 has resulted in 21.2million cases and 765 000 deaths (WHO situation report). One UK-based report identified 153 cases with neurological manifestations, of which 77 (62%) had a cerebrovascular event, 39 (31%) had altered mental status and 7 (4.58%) had encephalitis.<sup>2</sup> In a recent case series describing 24 patients with COVID-19-associated neurology, 9 patients fit the criteria for ADEM. Four of these patients had haemorrhagic changes seen on imaging.<sup>1</sup>

#### Acute disseminated encephalomyelitis

ADEM is a demyelinating inflammatory condition existing at the severe end of the spectrum of neurological manifestations in COVID-19. Clinical presentation is of a non-specific sudden onset encephalopathy, which may present as behavioural change or alteration in consciousness with or without fever. Neurological deficits are classically polyfocal and may include visual field

deficits and hemiparesis. A history of preceding viral infection is also supportive of the diagnosis.<sup>11</sup>

Bilateral and asymmetrical brain lesions on MRI in the supratentorial or infratentorial white matter are the radiological hallmark of this condition, which are hyperintense on T2-weighted and FLAIR sequences.<sup>12</sup> Typically, new clinical and radiological findings do not occur after 3 months of symptom onset.<sup>13</sup>

In this case, the patient's state of deep sedation means we cannot be certain when the condition developed. It may be significant that he received a 3-day course of high-dose steroids 2 weeks prior to the diagnosis of ADEM (due to severe sepsis). While no formal clinical trials have investigated the efficacy of steroids in ADEM, an observational study showed that early treatment with a short course of intravenous methylprednisolone, followed by a tapering steroid dose over a 4-week to 6-week period was associated with good outcomes in adults.<sup>13</sup> Early identification and treatment is therefore likely to be beneficial in this condition. It is also important to remember that, although ADEM is typically a monophasic illness, relapses can occur, and prolonged steroid courses may be warranted.<sup>14</sup>

### Learning points

- ▶ Clinicians treating COVID-19 should maintain a high index of suspicion for acute disseminated encephalomyelitis (ADEM) in patients who are slow to wake from sedation and who develop multifocal neurological symptoms.
- ▶ Observational data suggest early diagnosis and treatment of ADEM may improve prognosis for patients; therefore, a low threshold for obtaining MRI imaging is advised.
- ▶ Typical MRI brain lesions for ADEM are asymmetrical, bilateral and hyperintense on T2-weighted/fluid-attenuated inversion recovery sequences.
- ▶ Further studies are needed to better understand the spectrum of neurological manifestations associated with COVID-19 and their long-term effects.

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