**Supplementary Files**

**Acute Disseminated Encephalomyelitis and Acute Hemorrhagic Leukoencephalitis Following COVID-19: Systematic Review and Meta-Synthesis**

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SUPPLEMENTARY S1: Mass General Brigham Post-COVID-19 Case Vignettes

**Case #1**

Patient #1 is a 44-year-old man with a history of hypertension and polycythemia vera (not on treatment) who developed dyspnea, cough, decreased small, hypogeusia and hyposmia, found to be COVID-19 positive but was managed supportively at home. Twelve days from onset of COVID-related symptoms, he acutely developed new dysarthria. Diagnostic work-up was notable for an abnormal CT Chest consistent with known COVID-19 infection, persistently positive nasal swab COVID-19 RT-PCR and an abnormal brain MRI demonstrating supra- and infratentorial, diffuse FLAIR hyperintensities (Figure 2A-C) and areas of diffusion restriction without any associated hemorrhage burden. No spinal imaging was obtained. A lumbar puncture was unrevealing with no cells and normal protein (38 mg/dL; reference range 5-55 mg/dL), OCBs and IgG index were not performed. Serum anti-myelin oligodendrocyte glycoprotein (anti-MOG) and anti-aquaporin 4 (anti-AQP4) antibodies were not sent. No COVID-directed or immunotherapy for post-infectious ADEM were administered. The patient was discharged to an acute rehabilitation facility and subsequently lost to follow-up.

**Case #2**

Patient #2 is a 50-year-old man with a history of a remote left ACA-MCA infarct complicated by residual right-sided weakness (post-stroke mRS 2), who presented to our institution after an unwitnessed fall during the summer of 2020 with confusion and worsened aphasia and right hemiparesis relative to his baseline. Suspicion for seizure accounting for unwitnessed fall, prompted empiric treatment with levetiracetam. Initial imaging studies, including CT Head/C-spine/Chest/Abdomen/Pelvis and CT-angiography of the head and neck, revealed a hypodensity in the right parietal lobe with associated leftward midline shift and an incidental right renal lesion. Subsequent brain MRI revealed several, multifocal, supratentorial T2 FLAIR hyperintensities, some with associated contrast-enhancement and edema (Figure 2D-E). MRI of the cervical, thoracic and lumbar spine revealed three foci of intramedullary enhancement at C4-5, T3 and T12 levels (C-spine lesion shown in Figure 2F). No areas of FDG-avidity were evident on whole-body PET. A lumbar puncture yielded CSF with a lymphocytic pleocytosis (WBC’s 58 and 22 cells/µL in tubes 1 and 4, with 95%-97% lymphocytes), elevated protein (58 mg/dL; reference range: 5-55 mg/dL), normal glucose, elevated IgG index (1.14; normal: <0.85) and no oligoclonal bands at 80x concentration. Other CSF diagnostic studies that resulted negative were: bacterial culture, VDRL, *Toxoplasma gondii* IgG/IgM, ACE, anti-AQ4 antibody, flow cytometry and cytology. Serum anti-AQP4 and anti-MOG antibodies were negative. A brain biopsy of the right parietal lesion revealed histopathology consistent with an acute demyelinating process (Figure 3). Of note, immunohistochemistry stains for renal malignancy (*PAX8* and *CAIX*) were negative.  In pursuit of an infectious cause of ADEM amidst the current pandemic, a qualitative Roche Elecsys Anti-SARS-CoV-2 total antibodies test was performed and yielded a positive result consistent with prior infection. For neurologic-directed treatment, the patient received intravenous methylprednisolone (IVMP) 1g daily for five days followed by an oral prednisone taper of 60 mg daily with decrements of 10mg each week. He was discharged to a rehabilitation facility. Repeat MRI brain and spine performed 2-months from immunotherapy initiation demonstrated interval decrease in size of remaining lesions with complete resolution of others and no new areas of T2 FLAIR hyperintensities or contrast-enhancement. The patient was re-evaluated 6-months from time of discharge with minimal clinical improvement despite more evident radiographic improvement.

**Case #3**

Patient #3 is a 23-year-old man with history of autism spectrum disorder, chronic rhinitis, asthma, and obesity (BMI 38 kg/m2) who initially presented to an outside institution in late winter of 2020 for evaluation of persistent right lower face numbness, dizziness associated with nausea and vomiting, and concurrent binocular, positive visual phenomena, with onset approximately one-month after an unspecified viral illness. A nasopharyngeal swab for SARS-CoV-2 was positive. A brain MRI revealed innumerable, predominantly supratentorial T2-FLAIR hyperintensities, with many lesions displaying incomplete ring-enhancement. MRI C- and T-spine revealed a non-enhancing, T2/FLAIR hyperintense lesion at the level of the foramen magnum in the upper cervical cord with extension into the medulla. Lumbar puncture revealed unremarkable WBC count (1 cell; reference range <5/µL) and normal protein (45 mg/dL; reference range 5-55 mg/dL), however > 5 oligoclonal bands were present. No epileptiform features were found on EEG. Serologic testing was negative for: anti-MOG, anti-AQP4, JCV, SSA/SSB and Lyme. Empiric IVMP 1g daily for 3 days was administered and he was discharged to home without any discernible change in his neurologic symptoms. He was seen at our institution for outpatient follow-up and ocrelizumab was initiated with aim of preventing recurrent demyelinating event. Clinically, he has since developed seizures and is managed with levetiracetam monotherapy. Recent repeat brain MRI, approximately 1.5 months from initial presentation, showed interval enlargement and development of new T2/FLAIR hyperintense lesions, both supra- and infratentorially despite immunotherapy previously described and clinical stability (Figure 2G-I).

SUPPLEMENTARY S2: Case Demographics, Features of Antecedent COVID-19 Infection, and Neurologic Clinical Features. The method of COVID-19 infection confirmation is designated in parentheses in column 3 (COVID-19 Positivity). Delay to Neuro Onset refers to the interval duration from discovery of COVID-19 (by symptoms or laboratory confirmation) to the first manifestation of neurologic injury (symptoms or MRI abnormalities). Neuro onset acuity refers to the pace of development of the neurological symptoms leading to discovery of ADEM or AHLE. Abbreviations: PCR = SARS-CoV-2 PCR by nasopharyngeal swab; Antibody Serology = Anti-SARS-CoV-2 antibody positivity consistent with prior infection; AZM = azithromycin; CP = convalescent plasma; HCQ = hydroxychloroquine; INF = interferon; MGB = Mass General Brigham case series; N/A = not applicable; NR = not reported; Symp = symptomatic; U = unknown.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Case #** | **Age/**  **Sex** | **Confirmatory COVID-19 Diagnostics** | **COVID-19 Symp?** | **Level of Care**  **for COVID-19** | **COVID-19 Treatment** | **Delay to Neuro Onset** | **Neuro**  **Signs/**  **Symptoms** | **Neuro Onset Acuity** |
| 1e1 | 52/M | PCR | S | ICU | No | 22 | Encephalopathy | NR |
| 2e1 | 60/M | PCR | S | ICU | No | 27 | Encephalopathy | NR |
| 3e1 | 59/F | PCR | S | ICU | No | 10 | Encephalopathy,  Seizures,  Cranial neuropathy (impaired pupil reactivity OS) | NR |
| 4e1 | 47/F | Presumed | S | ICU | No | 8 | Encephalopathy,  Focal motor deficit,  Focal sensory deficit | NR |
| 5e1 | 54/F | Presumed | S | Floor | No | 14 | Encephalopathy,  Focal motor deficit, Cranial neuropathy (dysarthria)  Cerebellar (ataxia) | NR |
| 6e1 | 60/F | PCR | S | ICU | No | 18 | Encephalopathy | NR |
| 7e1 | 33/F | Presumed | S | ICU | No | 2 | Encephalopathy,  Focal motor deficit, Brainstem (abnormal respiratory pattern) | NR |
| 8e1 | 27/F | Presumed | S | Floor | No | 8 | Focal motor deficit, Focal sensory deficit, Cerebellar (gait unsteadiness) | NR |
| 9e2 | 33/M | PCR | S | ICU | No | 5 | Seizure,  Focal motor deficit, Focal sensory deficit | 3 days |
| 10e3 | 61/M | PCR | S | ICU | Remdesivir | 27 | Encephalopathy, Focal motor deficit | NR |
| 11e4 | 55M | PCR | S | ICU | No | 20 | Encephalopathy, Cranial neuropathy (ophthalmoplegia) | NR |
| 12e5 | 57/M | PCR | S | ICU | AZM, HCQ, lopinavir, ritonavir, anakinra | >12 | Encephalopathy, Brainstem (impaired VOR) | U, sedated |
| 13e6 | 56/M | PCR | S | ICU | No | U, sedated | Encephalopathy | U, sedated |
| 14e7 | 51/F | PCR | S | ICU | No | U, sedated | Encephalopathy, Brainstem (impaired VOR) | U, sedated |
| 15e8 | 49/M | PCR | S | ICU | No | U, sedated | Encephalopathy | U, sedated |
| 16e8 | 9/U | Antibody | A | Inpatient (not specified) | No | N/A | Encephalopathy, Focal motor deficit, Cranial neuropathy (ophthalmoplegia) | N/A |
| 17e9 | 71/M | PCR | S | ICU | “Stress-dose steroids” | U, insufficient reporting | N/A – no neurologic symptoms reported as patient remained on sedation until care withdrawal | U, insufficient reporting |
| 18e10 | 21/M | Antibody | S | ICU | No | ~18 | Encephalopathy, Focal motor deficit, Focal sensory deficit, Urinary retention | <24 hours |
| 19e11 | 1.4/F | PCR | S | ICU | No | U, insufficient reporting | Encephalopathy, Focal motor deficit, Cranial neuropathy (facial asymmetry), Cerebellar (truncal ataxia), Autonomic instability | U, insufficient reporting |
| 20e12 | 30/M | Antibody | A | Inpatient (not specified) | No | U, exposed ~28 days prior | Encephalopathy, Cranial neuropathy (INO OD) | 2 d |
| 21e13 | 64/F | Antibody | S | O | No | 21 | Focal sensory deficit, Cranial neuropathy (bilateral optic neuritis) | U, insufficient reporting |
| 22e14 | 53/M | PCR | S | ICU | No | U, sedated | Encephalopathy | U, sedated |
| 23e15 | 12/F | PCR | S | ICU | No | 5 | Focal motor deficit, Focal sensory deficit | 2 d |
| 24e16 | 59/F | PCR | S | ICU | HCQ | U, insufficient reporting | Encephalopathy, Focal motor deficit | 3 d |
| 25e16 | 41/M | PCR | S | ICU | No | U, sedated | Encephalopathy, Focal motor deficit | 6 d |
| 26e17 | 58/M | PCR | A | Inpatient (not specified) | N/A | U, A | Encephalopathy, Focal motor deficit | 30 d |
| 27e18 | 44/M | PCR | A | O | N/A | U, A | Encephalopathy, Focal motor deficit, Focal sensory deficit, Cranial neuropathy (dysarthria), Cerebellar (ataxia), Urinary retention | 2 d |
| 28e19 | 46/M | PCR | S | Floor | No | 35 | Encephalopathy, Focal motor deficit, Cranial neuropathy (left CN 7 palsy) | U, insufficient reporting |
| 29e20 | 37/F | PCR | S | ICU | HCQ, CP | U, sedated | Focal motor deficit | U, sedated |
| 30e20 | 56/M | PCR | S | ICU | CP | U, sedated | Encephalopathy | U, sedated |
| 31e20 | 70/F | PCR | S | ICU | CP | U, sedated | Encephalopathy | U, sedated |
| 32 MGB Under Review | 22/M | PCR | S | O | No | 56 | Encephalopathy, Focal motor deficit, Focal sensory deficit | < 24 hr |
| 33e21 | 1.1/F | PCR | S | ICU | No | 10 | Encephalopathy, Seizure | 10 d |
| 34e21 | 10/F | PCR | S | ICU | No | 6 | Encephalopathy, Focal motor deficit, Autonomic instability | 5 d |
| 35e22 | 51/F | PCR | S | ICU | Remdesivir | Uncertain, insufficient reporting | Seizure, Aphasia | U, insufficient reporting |
| 36e22 | 64/M | PCR | A | Inpatient (not specified) | Remdesivir, CP | U, sedated | Encephalopathy, Cranial neuropathy (dilated pupil OD) | U, sedated |
| 37e23 | 35/F | Antibody | S | O | No | 45 | Encephalopathy, Cerebellar (gait instability) | 6 d |
| 38e24 | 59/M | PCR | S | ICU | CP | 4 | Encephalopathy | U, sedated |
| 39e24 | 39/M | PCR | S | ICU | INF beta-1b, lopinavir, ritonavir | U, sedated | Encephalopathy | U, sedated |
| 40e24 | 73/M | PCR | S | ICU | INF beta-1b, lopinavir, ritonavir | 25 | Encephalopathy, Focal motor deficit | U, sedated |
| 41e25 | 6/M | PCR | A | O | No | U, A | Seizure | <24 hr |
| 42e26 | U/M | Confirmed (unspecified) | S | ICU | CP | U, sedated | Encephalopathy | U, sedated |
| 43e26 | U/M | Confirmed (unspecified) | S | ICU | Remdesivir | U, sedated | Encephalopathy | U, sedated |
| 44 MGB #1 | 44/M | PCR | S | O | No | 12 | Cranial neuropathy (dysarthria) | < 24 hr |
| 45 MGB #2 | 50/M | Antibody | A | O | No | U, A | Encephalopathy, Focal motor deficit,  Aphasia | < 24 hr |
| 46 MGB #3 | 23/M | PCR | S | O | No | 30 | Focal sensory deficit, Brainstem (area postrema) | Several days |

SUPPLEMENTARY S3: Case Diagnoses, Ancillary Testing, Treatments, and Outcomes. “Clinical Diagnosis” refers to the diagnosis made by the authors of the case report/series. “Path” refers to pathologically-confirmed diagnoses, either by biopsy or at the time of autopsy. “Nadir mRS” refers to the nadir mRS at the time of ADEM/AHLE presentation. Testing reporting is for CSF values (pleocytosis, elevated/high protein, and oligoclonal bands). “Last mRS” refers to the mRS at the last follow-up subsequent to the initial presentation.

Abbreviations: CN= cranial nerve; CYC = cyclophosphamide; Dx = diagnosis; Dex = dexamethasone; f/b = followed by; ICP = intracranial pressure monitoring; ID = insufficient data; INO = inter-nuclear ophthalmoplegia; IVIg = intravenous immunoglobulin; IVMP = Intravenous methylprednisolone; LETM = longitudinally-extensive transverse myelitis (>3 consecutive vertebral segments involved); LEV = levetiracetam; MCP = middle cerebellar peduncle; MGB = Mass General Brigham case; NCHCT = non-contrast head CT; PLEX = plasmapheresis; PO = oral administration; pred = prednisone; N/A = not applicable; NR = not reported; OD = *oculus dexter*; OS = *oculus sinister*; Pleo = CSF pleocytosis; QD = once daily; S.Seg. = short segment spinal lesions; TID = three times per day; VOR = vestibulo-ocular reflex.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Case** | **Clinical Dx/**  **Path** | **Nadir mRS** | **Brain MRI Findings** | **Spine MRI Findings**  **(Y/N),** *(LETM or S.Seg.)* | **Pleo (Y/N)** | **High Protein (Y/N)** | **OCBs**  **(Y/N)** | **Neuro Treatment** | **Last mRS** |
| 1e1 | AHLE | 5 | Involvement:  -Supratentorial  Findings:  -Multiple T2 FLAIR hyperintensities  -Areas of hemorrhagic foci  -Peripheral rim of restricted diffusion | N | N | N | N | N | ID, “improving” |
| 2e1 | AHLE | 5 | Involvement:  -Supratentorial  Findings:  -Multifocal T2 FLAIR hyperintensities  -Extensive subcortical microhemorrhages | N | N | N | NR | IVMP 1g QD x 3 days | ID, “improving” |
| 3e1 | AHLE | 6 | Involvement:  -Supratentorial  -Infratentorial (Brainstem)  Findings:  -T2 FLAIR hyperintensities  -Clusters of microhemorrhages -Restricted diffusion  -Peripheral rim enhancement | N | N | Y | NR | Dex (dosing not specified)  Others: LEV, acyclovir, CTX | 6 |
| 4e1 | AHLE/  Path | 5 | Involvement:  -Supratentorial  Findings:  -T2 hyperintensities  -Areas of contrast-enhancement  -Mass effect with midline shift, mild subfalcine herniation | N | N/A | N/A | N/A | IVMP 1g QD x 5 days f/b PO pred & IVIg  Right hemi-craniectomy | ID, “improving |
| 5e1 | ADEM | 4 | Involvement:  -Supratentorial  Findings:  -Multiple T2 hyperintense lesions  -Peripheral rim of restricted diffusion | N | Y | N | N | IVMP 1g QD x 3 days f/b PO pred | ID, “improving |
| 6e1 | ADEM | 5 | Involvement:  -Supratentorial  Findings:  -Multifocal T2 hyperintensities  -Areas of restricted diffusion | N | N | N | N | IVMP 1g QD x 3 days f/b PO pred | ID, “improving |
| 7e1 | ADEM | 5 | Involvement:  -Supratentorial  -Infratentorial (Brainstem)  Findings:  -Multifocal T2 hyperintensities  -Areas of restricted diffusion | Y, *LETM* | Y | N | N | IVMP 1g QD x 3 days f/b PO pred  Lumbar drain, ICP bolt | ID, “improving |
| 8e1 | ADEM | 3 | Involvement:  -Supratentorial  Findings:  -Diffuse, confluent T2 lesions  -Focus of restricted diffusion | Y, *S. Seg.* | N | Y | NR | N | 0 |
| 9e2 | AHLE | 5 | Involvement:  -Supratentorial  -Infratentorial (Brainstem)  Findings:  -T2 FLAIR hyperintensities  -Petechial hemorrhages  -Areas of restricted diffusion | Y,\* | N | N | NR | IVMP 1g QD x 5 days | 6 |
| 10e3 | AHLE | 5 | Involvement:  -Supratentorial  -Infratentorial (Cerebellum)  Findings:  -Multifocal FLAIR lesions  -Edema with midline shift  -Petechial hemorrhages  -Incomplete ring-like enhancement  -Limited areas of diffusion restriction | NR | N/A | N/A | N/A | IVMP 1g QD x 5 days & IVIg 2 g/kg & PLEX (1 session)  Mannitol | ID, “improving |
| 11e4 | AHLE | 5 | Involvement:  -Supratentorial  Findings:  -T2 FLAIR hyperintensities  -Areas of restricted diffusion | NR | N/A | N/A | N/A | “high-dose steroids” | ID, “improving |
| 12e5 | AHLE | 5 | Involvement:  -Supratentorial  Findings:  -T2 FLAIR hyperintensities  -Hemosiderin deposition within lesion | NR | N | Y | N | N | ID, “improving |
| 13e6 | AHLE | 5 | Involvement:  -Supratentorial  -Infratentorial (Brainstem & Cerebellum)  Findings:  -T2 FLAIR hyperintensities  -Diffuse hemosiderin within lesions  -Cystic hemorrhagic lesions | NR | N | Y | Y | N | NR |
| 14e7 | ADEM | 5 | Involvement:  -Supratentorial  Findings:  -T2 FLAIR hyperintensities  -Areas of restricted diffusion  -Mild enhancement in one lesion  -Intraventricular hemorrhage | NR | N | Y | N | IVMP 1g QD x 5 & IVIg 0.4 g/kg QD x 5 days | 3 |
| 15e8 | ADEM | 5 | Involvement:  -Supratentorial  -Infratentorial (Brainstem)  Findings:  -T2 FLAIR hyperintensities, all lesions with restricted diffusion | NR | NR | NR | NR | NR | NR |
| 16e8 | ADEM | ID | Involvement:  -Supratentorial  -Infratentorial (Cerebellar peduncles)  Findings:  -T2 FLAIR hyperintensities, all lesions with restricted diffusion  -Open-ring contrast-enhancement | NR | NR | NR | NR | NR | NR |
| 17e9 | ADEM/  Path | 5 | No neuroimaging obtained;  Post-mortem autopsy yielded diagnosis | N/A | N/A | N/A | N/A | NR | 6 |
| 18e10 | ADEM | 5 | Involvement:  -Supratentorial  -Infratentorial (Pontine)  Findings:  - T2 FLAIR hyperintensities | Y, *LETM* | Y | Y | NR | PLEX (250mL) QD x 5 days | 4 |
| 19e11 | ADEM | 4 | Involvement:  -Supratentorial  Findings:  -Diffuse, patchy T2 FLAIR lesions | N | N | Y | N | IVMP 30 mg/kg/d x 5 days & IVIg 2g/kg over 4 days | 0 |
| 20e12 | ADEM | 3 | Involvement:  -Supratentorial  Findings:  -T2 FLAIR lesions, contrast-enhancement | Y, *S. Seg.* | N | Y | Y | IVMP 1g QD x 5 days & rituximab 1g | NR |
| 21e13 | ADEM | 3 | Involvement:  -Supratentorial  Findings:  -Nodular T1 contrast-enhancing lesions -Bilateral optic nerve enhancement | Y, *S. Seg.* | Y | Y | Y | IVMP 1g QD x 5 f/b PO pred taper (starting dose: 75 mg/d) & IVIg 2 g/kg over 5 days | 1 |
| 22e14 | AHLE | 5 | Involvement:  -Supratentorial  Findings:  -T2 FLAIR lesions with central diffusion restriction  -Intraventricular hemorrhage, diffuse parenchymal microhemorrhages | N/A | NR | N | Y | IVMP 1g QD x 3 days f/b PO pred taper (starting dose: 60mg/day) | 2 |
| 23e15 | ADEM | 5 | Involvement:  -Supratentorial  Findings:  - T2 FLAIR lesions, restricted diffusion | Y, *LETM* | N | N | NR | IVMP 1g QD x 5 days administered twice for total 10-day course | 4 |
| 24e16 | ADEM | 5 | Involvement:  -Supratentorial  -Infratentorial (Cerebellum)  Findings:  - T2 FLAIR lesions, restricted diffusion | NR | N | N | N | N | 6 |
| 25e16 | AHLE | 5 | Involvement:  -Supratentorial  Findings:  - T2 FLAIR lesions, restricted diffusion -One lesion with microhemorrhage | N | N | N | N | N | 2 |
| 26e17 | ADEM | 6 | Involvement:  -Supratentorial  -Infratentorial (Brainstem)  Findings:  - T2 FLAIR lesions | N/A | N | N | N | Dex 8mg TID | 6 |
| 27e18 | ADEM | 4 | Involvement:  -Supratentorial  Findings:  - T2 FLAIR lesions, some with homogenous contrast-enhancement | Y, *S. Seg.* | Y | N | N | IVMP & IVIg (dosing not specified) | NR |
| 28e19 | AHLE | 4 | Involvement:  -Supratentorial  -Infratentorial (Brainstem)  Findings:  - T2 FLAIR lesions, some with diffusion restriction  -Most with irregular rim-enhancement  -Few microhemorrhages | N | Y | Y | NR | “steroids for 5 days” | 6 |
| 29e20 | ADEM | 4 | Involvement:  -Supratentorial  -Infratentorial (Brainstem)  Findings:  - T2 FLAIR lesions, with diffusion restriction  -Some contrast-enhancing lesions | N | N | Y | N | Dex 20mg x 5 days f/b Dex 10mg x 5 days | 4 |
| 30e20 | ADEM | 5 | Involvement:  -Supratentorial  -Infratentorial (Cerebellum)  Findings:  - T2 FLAIR lesions, several with diffusion restriction | NR | N | Y | N | IVMP 1g QD x 5 days & IVIg 25g/d x 3 days | 5 |
| 31e20 | ADEM | 5 | Involvement:  -Supratentorial  -Infratentorial (Brainstem, MCP)  Findings:  - T2 FLAIR lesions, most with diffusion restriction  -Minimum enhancement | NR | N | Y | Y | IVMP 1g QD x 5 days & IVIg 25g/d x 3 days | 5 |
| 32 MGB Under Review | AHLE | 5 | Involvement:  -Infratentorial (Brainstem)  Findings:  - T2 FLAIR lesions, patchy areas of restricted diffusion  -Heterogeneous enhancement  -Punctate hemorrhages in medulla | Y, *LETM* | N | N | N | IVMP 1g QD x 5 days & IVIg 2g/kg & PLEX (5 sessions) & CYC | 4 |
| 33e21 | ADEM | 5 | Involvement:  -Supratentorial  -Infratentorial (Brainstem)  Findings:  - T2 FLAIR lesions with restricted diffusion | NR | Y | NR | NR | “steroids” | 2 |
| 34e21 | ADEM | 5 | Normal brain MRI 6 days following neurologic symptom onset. However, interval brain MRI, 50 days from neurologic disease onset, revealed:  Involvement:  -Supratentorial  Findings -Multifocal T2 hyperintensities | N | Y | Y | NR | NR | 2 |
| 35e22 | ADEM/  Path | 6 | No imaging obtained as patient deceased; Diagnosis made via post-mortem autopsy | NR | N/A | N/A | N/A | NR | 6 |
| 36e22 | AHLE/Path | 6 | No brain MRI obtained; NCHCT showed parenchymal hemorrhage | NR | N/A | N/A | N/A | N | 6 |
| 37e23 | ADEM | 5 | Involvement:  -Supratentorial  -Infratentorial (Not further specified)  Findings:  - T2 FLAIR lesions | NR | N | N | NR | IVMP 1mg/kg x 5 days & IVIg 2g/kg x 3 days, later PLEX (5 sessions) | 5 |
| 38e24 | ADEM | 5 | Involvement:  -Supratentorial  -Infratentorial (Brainstem & Cerebellum)  Findings:  -Multiple, ill-defined, fluffy T2 FLAIR hyperintensities  -Microhemorrhages  *Note: No contrast due to renal failure* | Y, *LETM* *&* *S. Seg.* | Y | Y | N | IVIg 2g/kg for 3 total courses administered at 3-week intervals | 4 |
| 39e24 | ADEM | 3 | Involvement:  -Supratentorial  Findings:  -Bilateral non-enhancing FLAR lesions  -Microhemorrhages | NR | Y | Y | NR | N | NR |
| 40e24 | ADEM | 5 | Involvement:  -Supratentorial  Findings:  -Non-enhancing, confluent and extensive T2 FLAIR hyperintensities with restricted diffusion and associated edema  -Microhemorrhages  -Evolved infarcts | NR | N | Y | NR | “High-dose steroids” | 6 |
| 41e25 | ADEM | 1 | Involvement:  -Supratentorial  -Infratentorial (Cerebellum)  Findings:  -Multiple T2 hyperintensities, all with contrast-enhancement | NR | N | N | Y | IVMP 30mg/kg/day x 5 days f/b PO pred taper | 0 |
| 42e26 | ADEM | 5 | Involvement:  -Supratentorial  Findings:  -T2 hyperintensities | Y, *S. Seg.* | Y | Y | NR | IVIg | NR |
| 43e26 | AHLE | 5 | Involvement:  -Not specified  Findings:  -Multifocal hemorrhagic lesions with predominant white matter involvement | NR | NR | NR | NR | IVIg & “corticosteroids” | NR |
| 44 MGB #1 | ADEM | 1 | Involvement:  -Supratentorial  -Infratentorial (Cerebellum)  Findings:  -T2 FLAIR lesions with areas of restricted diffusion | N/A | N | N | N/A | N | NR |
| 45 MGB #2 | ADEM/Path | 5 | Involvement:  -Supratentorial  -Infratentorial (Cerebellum)  Findings:  -T2 FLAIR lesions, some with contrast-enhancement and perilesional edema | Y, *S. Seg.* | Y | Y | N | IVMP 1g QD x 5 days f/b PO pred taper (starting dose 60mg with weekly 10mg decrements) | 4 |
| 46 MGB #3 | ADEM | 2 | Involvement:  -Supratentorial  -Infratentorial (Brainstem)  Findings:  -Innumerable T2 FLAIR hyperintensities, many with incomplete-ring contrast-enhancement | Y, *S. Seg.* | N | N | Y | IVMP 1g QD x 3 days  Ocrelizumab started during outpatient visit | 1 |

\*Complete spinal imaging not done.

SUPPLEMENTARY S4: Supplementary References for Included Case Series and Case Reports

e1. Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain.* 2020;143:3104-3120.

e2. Handa R, Nanda S, Prasad A, et al. Covid-19-associated acute haemorrhagic leukoencephalomyelitis. *Neurol Sci.* 2020;41:3023-3026.

e3. Yong MH, Chan YFZ, Liu J, et al. A rare case of acute hemorrhagic leukoencephalitis in a COVID-19 patient. *J Neurol Sci.* 2020;146:117035.

e4. Green C, Morrison H, Smith P, et al. Teaching Neuroimages: COVID-19-associated acute disseminated encephalomyelitis with corpus callosal hemorrhage. *Neurology.* 2021;96:e307-e308.

e5. Karapanayiotides T, Geka E, Prassopoulos P, et al. Concentric demyelination pattern in COVID-19-associated acute haemorrhagic leukoencephalitis: a lurking catastrophe? *Brain.* 2020;143:1-4.

e6. Haqiqi A, Samuels TL, Lamb FJ, Moharrum T, Myers AE. Acute haemorrhagic leukoencephalitis (Hurst disease) in severe COVID- 19 infection. *Brain Behav Immun Health.* 2021;12:100208.

e7. Parsons T, Banks S, Bae C, Gelber J, Alahmadi H, Tichauer M. COVID-19-associated acute disseminated encephalomyelitis (ADEM). *J Neurol.* 2020;267:2799-2802.

e8. Assunção FB, Fragoso DC, Scoppetta TLPD, Maia ACM. COVID-19-associated acute disseminated encephalomyelitis-like disease. *Am J Neuroradiol.* 2021;42:E21-E23.

e9. Reichard RR, Kashani KB, Boire NA, Constantopoulos E, Guo Y, Lucchinetti CF. Neuropathology of COVID-19: a spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology. *Acta Neuropathol.* 2020;140(1):1-6.

e10. Zoghi A, Ramezani M, Roozbeh M, Darazam IA, Sahraian MA. A case of possible atypical demyelinating event of the central nervous system following COVID-19. *Mult Scler Relat Disord.* 2020;44:102324.

e11. McLendon LA, Rao CK, da Hora CC, Islamovic F, Galan FN. Post-COVID-19 acute disseminated encephalomyelitis in a 17-month-old. *Pediatrics.* 2021;24:e2020049678.

e12. Shahmirzaei S, Moghadasi AN. Association of COVID-19 and acute disseminated encephalomyelitis (ADEM) in the absence of pulmonary involvement. *Autoimmun Rev.* 2021;20(3):102753.

e13. Novi G, Rossi T, Pedemonte E, et al. Acute disseminated encephalomyelitis after SARS-CoV-2 infection. *Neurol Neuroimmunol Neuroinflamm.* 2020;7:e797.

e14. Langley L, Zeicu C, Whitton L, Pauls M. Acute disseminated encephalomyelitis (ADEM) associated with COVID-19. *BMJ Case Rep.* 2020;13:e239597.

e15. de Miranda Henriques-Souza AM, de Melo ACMG, Madeiro BACS, Freitas LF, Rocha-Filho PAS, Gonçalves FG. Acute disseminated encephalomyelitis in a COVID-19 pediatric patient. *Neuroradiology.* 2021;63:141-145.

e16. Lopes CCB, Brucki SMD, Passos Neto CEB, et al. Acute disseminated encephalomyelitis in COVID-19: presentation of two cases and review of the literature. *Arq Neuropsiquiatr.* 2020;78(12):805-810.

e17. Abdi S, Ghorbani A, Fatehi F. The association of SARS-CoV-2 infection and acute disseminated encephalomyelitis without prominent clinical pulmonary symptoms. *J Neurol Sci.* 2020;416:117001.

e18. Utukuri PS, Bautista A, Lignelli A, Moonis G. Possible acute disseminated encephalomyelitis related to severe acute respiratory syndrome coronavirus 2 infection. *Am J Neuroradiol.* 2020;41:E82-E83.

e19. Varadan B, Shankar A, Rajakumar A, et al. Acute hemorrhagic leukoencephalitis in a COVID-19 patient-a case report with literature review. *Neuroradiology.* 2021;63:653-661.

e20. McCuddy M, Kelkar P, Zhao Y, Wicklund D. Acute demyelinating encephalomyelitis (ADEM) in COVID-19 infection: a case series. *Neurol India.* 2020;68:1192-1195.

e21. Vraka K, Ram D, West S, et al. Two paediatric patients with encephalopathy and concurrent COVID-19 infection: two sides of the same coin? *Case Rep Neurol Med.* 2021;6658000.

e22. Walker JM, Gilbert AR, Bieniek KF, Richardson TE. COVID-19 patients with CNS complications and neuropathologic features of acute disseminated encephalomyelitis and acute hemorrhagic leukoencephalopathy. *J Neuropathol Exp Neurol.* 2021;00(0):1-4.

e23. Kumar A, Olivera A, Mueller N, Howard J, Lewis A. Delayed SARS-COV-2 leukoencephalopathy without severe hypoxia. *J Neurol Sci.* 2020;418:117146.

e24. Umapathi T, Quek WMJ, Yen JM, et al. Encephalopathy in COVID-19 patients; viral, parainfectious, or both? *eNeurologicalSci.* 2020;21:100275.

e25. Manzo ML, Galati C, Gallo C, et al. ADEM post-Sars-CoV-2 infection in a pediatric patient with Fisher-Evans syndrome. *Neurol Sci.* 2021;12:1-4.

e26. Koh JS, de Silva DA, Quek AML, et al. Neurology of COVID-19 in Singapore. *J Neurol Sci.* 2020;418:117118.